OEHHA Responses, Final

Revised Noncancer TSD and Six RELS: Public Comments received 2/1/08

Commenter	Page	TSD	Acet-aldehyde	Acrolein	Arsenic	Form-aldehyde	Mn	Hg
American Chemistry Council	2	X						
American Forest & Paper Association	10		X	X				
BAAQMD	13	X						
Cal/CIMA and CCMEC	15	X			X		X	X
Exponent for ACC etc.	33	X	X	X	X	X	X	X
Formaldehyde Council	45					X		
LA Unified School Dist.	74	X						
Long Beach USD	76	X						
Herman Miller Inc.	78					X		
Manganese Interest Group		X					X	
NRDC	80	X					X	X
TERA	89	X						
W. Berkeley Alliance	94	X					X	

Comments of Richard A. Becker Ph.D., on behalf of the American Chemistry Council.

Comment 1:

Introduction: As a fundamental principle, the Council and its members support health, safety, and environmental protection policies that incorporate risk-based priorities and cost-effective risk management. The risk assessments that are integral to this process should provide objective, realistic, and scientifically balanced analysis. Even the most complete and data-derived risk analysis will require "inferential bridges" or "risk assessment policy" to fill data gaps and scientific uncertainties. This does not mean, however, that it is acceptable to ultimately manage risk based on unjustified assumptions and policies that generate unrealistically high or exaggerated risk assessments. In short, risk assessments should not "intermingle" important policy judgments within the scientific assessment of risk. Risk assessments should aspire to the greatest extent possible to be objective scientific exercises that seek to realistically estimate risk. Risk management comes later, and must be fully and transparently distinguished from risk assessment if the practice of risk assessment is to have scientific credibility.

Response:

OEHHA's draft guidelines clearly lay out the principle that where quantitative and data-based descriptions of toxic responses and the extrapolations necessary to derive health-protective Reference Exposure Levels are available, these will be used. In the partial or complete absence of such evidence, uncertainty factors will be applied. Where this uncertainty cannot be quantified by examination of the specific data, default values as suggested by NRC (1994) are recommended in the guidelines. The commenter's suggestion that policy judgments should not be "intermingled' within a scientific risk assessment is not meaningful: clearly most risk assessments in practice will use a combination of specific data where available, and default assumptions where more specific data are not available. The draft guidelines go to considerable lengths to establish such default values based on analogy with specific examples where data are available.

Comment 2:

OEHHA's *"Technical Support Document for the Derivation of Noncancer Reference Exposure Levels"* outlines the Office's methodology for developing acute, 8-hour, and chronic health protective levels or Reference Exposure Levels (RELs) to be used by California's Air Toxics Hot Spots and Toxic Air Contaminants programs. Citing SB25, OEHHA proposes a significant change to the REL derivation methodology based on OEHHA's perception that the existing methodology for extrapolation using uncertainty factors (typically 10X interspecies multiplied by 10X intraspecies) somehow falls short in assuring that infants and children are adequately protected.

Response:

The Children's Environmental Health Protection Act ("SB25") required OEHHA to examine the question of whether the existing methodology was adequate to protect infants and children. It was OEHHA's examination of available data which led to the conclusion that the existing methodology was, under some circumstances, inadequate and that revised guidelines were therefore necessary.

Comment 3:

In the Office's November 2007 draft, OEHHA proposes that REL derivation use either chemical-specific physiologically-based pharmacokinetic modeling or a newly-proposed 30X intraspecies uncertainty factor $(UF_H)_3$ for infants and children. OEHHA provides details on an analysis it has performed to examine the magnitude of differences between infants and children and adults with respect to chemical toxicokinetics[4], and uses this as support for proposing a 30X default uncertainty factor (human) for infants and children. Although it is true that scientific studies have shown that there are quantifiable differences in the absorption, distribution, metabolism, and elimination of various chemicals in infants/children and adults, OEHHA's analysis and discussion in the document has failed to address key issues relating to use of uncertainty factors in chemical risk assessment. Therefore OEHHA has not adequately and scientifically justified its proposal to adopt a 30X default UF_H.

Response:

OEHHA agrees with the commenter that there can be significant differences in toxicokinetics between adults and infants or children. However, OEHHA considers that the proposals in the draft revised guidelines are scientifically justified, and that adequate explanation has been provided.

Comment 4:

The range of variability and sensitivity encompassed by uncertainty factors is not fully appreciated in OEHHA's proposal to increase the default uncertainty factor (human).

Review of the published literature and regulatory documents reveals that many risk assessors have failed to appreciate what the 10X interspecices factor and the 10X intraspecies uncertainty factor (UF_H) actually represent. As discussed by Dourson et al. (2002), the UF_H is routinely applied in risk assessment to a toxicity value such as a human equivalent no-observed adverse effect level (NOAEL) or a benchmark dose (BMD). Such values - human equivalent NOAELs or human equivalent BMDs - are extrapolated using the 10X interspecies UF and are representative of a response within the low end (the most sensitive population) of the normal distribution of the overall human population. Then the UF_H is applied to the human equivalent NOAEL or human equivalent BMD. With this approach -- starting from the low end (most responsive) of the normal range of human response -- the risk assessor is actually accounting for overall variability in the human population of much more than 10-fold. As described in Dourson et al. (2002), the overall variability within the human population that is taken into account in this standard risk assessment methodology is more in the range of 100- to 1000-fold. This is illustrated below, in

Attachment 1. "Figure 6 from Dourson et al., 2002." By not addressing this important issue in interpretation of the intraspecies uncertainty factor, and how this also accounts for variability in the human population, OEHHA has developed an approach for the UF_H that is scientifically inconsistent. In Dourson et al., 2002, the authors explain how the 10X intraspecies UF_H accounts for overall variability in the human population of 100- to 1000-fold. OEHHA's modeled inter-individual variability indicated a range from 1 to 720 for a specified set of chemicals, and this range is actually consistent with the analysis of Dourson et al, 2002. Where OEHHA differs is in their proposal to increase the UF_H to 30X, whereas Dourson and co-authors (2002) conclude that the standard 10X UF_H already encompasses concerns for this degree of human variability so there is no need to increase the UF.

Dourson et al. (2002) reviewed the issue of differential risk between adults and infants and children. As stated by the Dourson et al, 2002, "virtually all studies available suggest that a high percentage of the population, including children, is protected by using a 10- fold uncertainty factor for human variability or by using a 3.16-fold factor each for toxicokinetic and toxicodynamic variability. Based on specific comparisons for newborns, infants, children, adults, and those with severe disease, the population protected is between 60 and 100%, with the studies in larger populations that include sensitive individuals suggesting that the value is closer to 100%." With respect to the lower value, 60%, it is important to consider this value in light of its derivation from those with severe disease; thus it does not really reflect typical variability. Dourson and co-authors (2002) demonstrate how the standard UF_H of 10X already accounts for human variability in the range of 100 to 1000-fold. They point out that "[P]erhaps the strongest studies from which to draw reasonable and general conclusions are those of Renwick and Lazarus (1998) and Hattis *et al*. (1999a,b). Both groups of investigators worked from large databases that included both kinetic and dynamic parameters and evaluated normal and sensitive populations, including children. The conclusion of both groups is that a UF_H of 10 is likely to protect 99.9% or more of the population, and this population includes children."

Clearly, based on the comprehensive analysis of Dourson et al., 2002, the practice of risk assessment using the standard uncertainty factors (UF_A, UF_H, UF_D and UF_S)$_5$ is both precautionary and health protective, for systemic, reproductive and developmental toxicants for both adults and children,.

Response:

OEHHA does not regard the publication by Dourson et al. *(2002) as consistent with more recent work on the subject of uncertainty and variability in human response. These authors presented an extensive analysis concluding that the current UF_H as being adequate for all members of an exposed population including children and infants. In their Table 3 they present a list of U.S.EPA RfD's presumably indicating the adequacy of UF_H values of 10 or less over a wide range of chemicals. Renwick & Lazarus (1998) reviewed 47 drugs but only 2 involved inhalation exposures. They estimated that a UFHK of 3.16 would not cover 0.9% of an exposed population if response was log-normally distributed. We do not believe these results seriously conflict with our conclusion, especially in view of the lack of the relevant exposure route and the nature of the chemicals studied. Hattis et al. (1999) looked at human interindividual variability of a number of parameters related to health risks: those related to inhalation risks in children are the breathing rates per kg BW. We do not see that the data presented conflict with our*

proposal. OEHHA's specific concern is that in the case of neonatal and young infants, the UF_{H-k} of √10 is probably inadequate for inhalation exposure. A number of published analyses of human data and predictions from modeling indicate that an increase of the UF_{H-k} to 10 would be prudent in those cases where insufficient data are available. For example, the following studies support OEHHA's proposal. A limitation of the available data is that relatively few studies have focused on inhalation exposure and predictive PBPK analyses have limitations as well.

1. *Renwick (1998) and Renwick et al. (2000) compared age-related differences in the pharmacokinetics of 36 drugs which are eliminated by different processes. Renwick et al. (2000) concluded that the main factor affected by age was the overall difference in clearance and the resulting elevated internal dose in neonates and children compared to adults. While these authors concluded that a UF_H value of 100 was not justified, they noted that an additional factor (>10) might be necessary in the case of a lack of developmental and reproductive toxicity data, inadequate data, or an irreversible toxic effect in neonates/young animals.*

2. *Dorne et al. (2001) evaluated the validity of the √10 UF_{HK} in relation to CYP1A2 metabolism using published data for clearance (CL), AUC and peak plasma concentration (Cmax) for caffeine, theophylline, theobromine, paraxanthine, and R-warfarin in human volunteers. The authors identified subgroups for which the √10 would be inadequately protective including about half of pregnant women, nearly all neonates, and 13% of infants. These drugs were administered orally or parenterally.*

3. *Ginsberg et al. (2002) also evaluated child/adult pharmacokinetic differences in the drug literature. These authors identified about 100 chemicals with some pharmacokinetic data and analyzed a subset of 45. Multiple regression analysis was used to evaluate relationships between age groups and mean pharmacokinetic parameter (Cmax, half-life, AUC, volume of distribution, clearance). In general, for many chemicals, early life stages appeared different in terms of clearance, half-life, and volume of distribution. The overall study results indicate that premature and full-term neonates tended to have 3 to 9 times longer half-life than adults for the drugs studied. Like the earlier work of Renwick et al. (2000) and Dorne et al. (2001) the drugs studied were administered orally or parenterally, not by inhalation.*

4. *Pelekis et al. (2001) used a PBPK model to derive adult and child pharmacokinetic UFs for a group of volatile organic compounds (VOCs). Adult models (50 and 90 kg) were compared with a 10kg child model. Simulations involved continuous exposure to 1 ppm VOC for 30 days. Arterial, venous and tissue concentrations of the parent VOCs were used to calculate Adult/Child values. For the Liver concentration metric the Adult/Child values were: styrene (0.033); xylene (0.037); trichloroethylene (0.061); dichloromethane (0.092); and chloroform (0.11). The model predictions indicate up to a 30-fold higher concentration of VOCs in child liver than adult liver. Unlike the drug studies above this modeling study involves inhalation exposure of relevant environmental toxicants.*

5. *Jonsson and Johanson (2001) used a PBPK model of dichloromethane (DCM) to study the influence of metabolic polymorphism on cancer risk estimates. Exposure was by inhalation and metabolism by glutathione transferase theta (GSTT1) and mixed function*

oxidases (MFO) occurred in lung and liver. The model was fitted to published toxicokinetic data on 27 male volunteers exposed to 250-1000 ppm DCM. Excess cancer risk resulting from lifetime exposures to 1-1000 ppm DCM was estimated using Bayesian and Monte Carlo methods. The relevant dose metric was DNA-protein cross links (DPX) in liver derived from DCM metabolized via the GSTT1 pathway. Data on the frequencies of the three GSTT1 genotypes (0/0, +/0, +/+) in the Swedish population were used in the analysis. The results indicated a large interindividual variability in estimated risk, even within the two metabolizing groups (+/0, +/+). The results indicate that the UF_{HK} of √10 for human PK variability may not be adequately protective for non-cancer endpoints. One percent of the population would not be covered by a UF_{HK} of 4.2-7.1 and 0.1 percent would not be covered by a UF_{HK} of 7.3-14.5. While this study focuses on adults the results may apply even more strongly to infants and young children where inhalation may result in greater exposures per unit body weight, and metabolic systems, particularly MFO enzymes, are still under development.

6. *Ginsberg et al. (2004) used PBPK modeling to evaluate the difference between neonates and adults in the metabolism of theophylline and caffeine. Both chemicals are metabolized by CYP1A2: caffeine to theophylline, theobromine, and paraxanthine; and theophylline to 3-methylxanthine, 1-methyluric acid, and 1,3-dimenthyluric acid. In neonates theophylline is "back" methylated to caffeine. Caffeine is cleared much more slowly in neonates than in adults (0.15 vs. 1.57 mL/kg-min, respectively) whereas theophylline is similarly cleared (0.35 vs. 0.86 mL/kg-min, respectively). The authors concluded that the extra back methylation path in neonates could largely account for the differences seen between neonates and adults. The results emphasize the importance of different metabolic pathways operating in neonates and infants during development.*

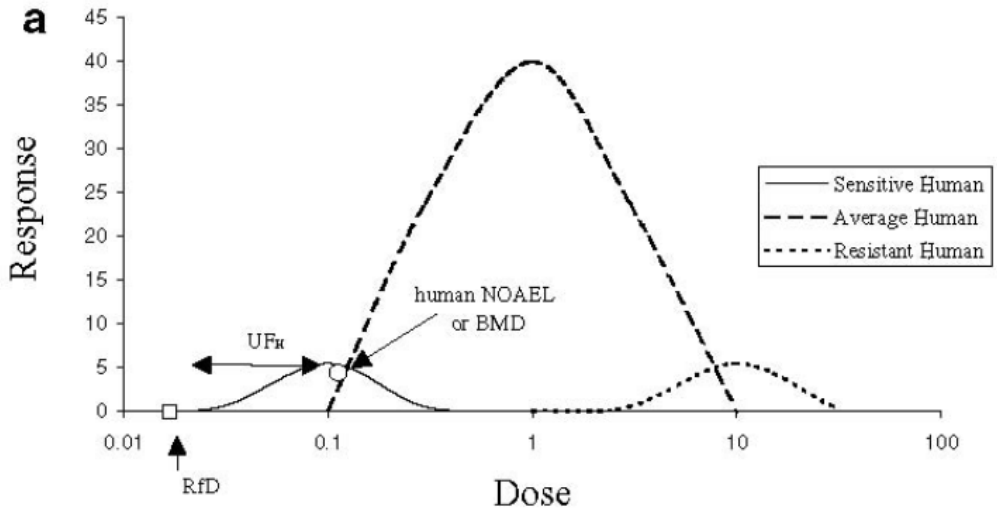
7. *Gentry et al. (2003) evaluated the impact of pharmacokinetic differences on tissue dosimetry during pregnancy and lactation with PBPK modeling. Six chemicals were investigated: isopropanol, vinyl chloride, DCM, perchloroethylene, nicotine, and TCDD. Model predicted differences in dosimetry during pregnancy were largely the result of the development of metabolic pathways in the fetus or changes in tissue composition in mother and fetus. Generally, predicted blood concentrations were lower in the neonate during lactation than in the fetus during gestation. Predicted fetal/neonatal exposures vs. maternal exposures ranged from 2-fold greater (TCDD) to several orders of magnitude lower (isopropanol). The results of this study are in general agreement with earlier studies namely that the "age range of greatest concern is clearly the perinatal period. The most important factor appears to be the potential for decreased clearance of toxic chemicals … due to immature metabolic enzyme systems".*

Several aspects of the analysis by Dourson et al. *are questionable. Problems with their interpretation include the following*:

1. *The paper confuses variability (i.e., measurable differences between individuals in a group or population), which <u>may</u> be represented by the log-normal distributions shown in their figures, and uncertainty (the range of plausible values for a parameter which has not been, or cannot be directly measured), which almost certainly is not distributed in this way.*

2. *OEHHA disagrees with the assumption that the "human equivalent response" distribution from which they identify a NOAEL has any relationship to the distribution of responses in an actual human population. If the study on which the derivation is based is in fact a human study (clinical or epidemiological), then this distribution may be reflective of a human population, although not necessarily the one of interest to the risk assessor. However, in the majority of cases the basis study is in animals. These data by definition contain no information about human variability, especially since the test animals are age-selected, and laboratory rodents in particular are genetically homogeneous and therefore much less variable than a human population.*

3. *Dourson* et al.*'s Figure 6a (below) shows three distributions of response vs. dose for sensitive, normal and insensitive populations.*



*The claim is that the normal UF_H based on a criterion (BMD or NOAEL) determined in the **normal** population covers perhaps a 1000 fold dose range of the total human population including those of abnormal sensitivity. This example does not directly address the adequacy of the UF_H for determining a health protective exposure criterion for infants and children based on a toxicity observed in a normal human or animal study. In this figure, it is implied that at least half of the sensitive human subgroup (which could be young children) would respond at a dose ten times lower than the "average human".*

4. *Even if the shapes of the actual dose/ response distributions shown in their Figure 6a resemble the assumed log-normal shape in the vicinity of the ED50, there are unlikely to be any data to support the conclusion that this shape is followed out to doses several decades above or below the ED50 as assumed by Dourson et al. (2002). Indeed, such very limited data as have a bearing on this question, such as distributions of common physiological or structural characters, imply the opposite: that the assumed distribution shape breaks down at extreme values.*

5. *In considering the interindividual differences between humans of different ages, the analysis by Dourson et al. is inapplicable because it assumes that the variability (and*

uncertainty) within the human population is represented by a single log-normal distribution. It has been emphasized so often that it has become a cliché to point out that "children are not just small adults". A necessary corollary to this is that their susceptibility is not represented by merely a percentile within the overall adult distribution, but rather by an entirely separate (probably also log-normal) distribution with its own geometric mean and standard deviation or, rather, several such distributions reflecting the properties of different age groups having distinctly different susceptibility and variability. Especially for sub-groups such as infants, who have markedly different anatomical, physiological and biochemical characteristics from adults, this separate distribution may be widely separated from the log-normal distribution representing adults. This is in essence what we observed with our investigation of PBPK models with infant- or child-specific parameters.

6. *The attempt to equate a reference exposure level with some specific frequency point on a distribution is intrinsically unsound. Not only are the actual distributions of variability and uncertainty generally unknown, and their additivity (or otherwise) not established, but the general objective in defining a reference exposure level is to select a level at which no effects are expected in the general population, not a level at which a specified low level of response such as 1% or 5% is expected. As noted in the document, a NOAEL is not a threshold, but rather an exposure level without observable response. Since these are usually based on animal studies, the response rate at the NOAEL can in fact range from 1% in a large study to 20% in a small one (Gaylor, 1992; Leisenring and Ryan, 1992). The assumption for non-cancer risk assessments is that there is a true threshold below which no responses are expected, and the objective in setting the reference exposure level is to choose a level below that threshold.*

Comment 5:

OEHHA's discussion of intraspecies variability and the magnitude of UF_H is incomplete.

Review of the document reveals that OEHHA has failed to consider some key studies that have examined the ability of the 10X UF_H to adequately account for differences in toxicity response between healthy adults and infants and children. As indicated above, the comprehensive review by Dourson et al., 2002 is a key peer reviewed publication that speaks directly to the issue of adequacy of uncertainty factors in children's health risk assessments. Failure to review or analyze this publication is a critical omission by OEHHA. In addition, the OEHHA document fails to discuss the findings of several individual studies such as Hattis et al. (1999a, 1999b), Renwick (1998), Naumann (2001), Skowranski and Abdel-Rahman (2001), and Renwick et al. (2001). By focusing only on studies that examine the toxicokinetics of chemicals, the Agency has failed to consider papers that have reviewed and analyzed both kinetics and dynamics as a function of age. Importantly, these studies all conclude that the 10X UF_H is adequate to ensure protection of infants and children as well as other sensitive human subpopulations.

Response:

OEHHA has reviewed the papers cited above (in the response to comment 4) and others, which are the most relevant and up-to-date publications on the subject of age dependence, as well as

conducting original work on the problem. The citations given in the main technical support document and its appendices are much more numerous and many are more recent than those mentioned in this comment. In particular, other more extensive publications by Hattis, Renwick and colleagues are discussed. Most of OEHHA's discussion relates to the toxicokinetic aspect of UF_H because that is where there are sufficient data to make a general recommendation. As noted in the document, we find that whereas there are a few individual examples where the age-dependence of toxicodynamics has been explored there is a lack of generally applicable knowledge in this area.

Comment 6:

Conclusions: Increasing the UF_H, as proposed by OEHHA, would make the REL risk assessment methodology less science-based, at odds with the historical standard practice of risk assessment, unnecessarily more conservative, and overly precautious. OEHHA's proposal to require use of UF_H of 30X appears to arise from a fundamental misunderstanding of the concept and application of UFs. Prior to moving forward withthe proposed change, OEHHA should convene a workshop of experts in both toxicokinetics and human health risk assessment to 1) explore OEHHA's assumptions re: UF_H in greater detail 2) evaluate the peer reviewed published findings that, taken together, show that the 10X interspecies factor and the 10X intraspecies uncertainty factor (UF_H) cover human variability of more than 10-fold and that variability in the range of 100-1000 is already inherent in existing, standard risk assessment methodology and practice.

Response:

OEHHA has proposed revisions to the REL risk assessment methodology because we find that the "historical standard practice of risk assessment" may be inadequate in certain respects. Given that the key problem addressed by the use of default uncertainty factors is the uncertainty present where data and adequate conceptual models are lacking, it is incorrect to assert that the proposals are "unnecessarily more conservative, and overly precautious (sic)*". OEHHA has ensured that the guidelines provide methodology for using chemical specific data when available. The default UFs are to be applied when the data are absent or insufficient, which is most often the case.*

The expert review of OEHHA's proposals advocated by the commenter is provided by the Scientific Review Panel. OEHHA looks forward to receiving and acting on its input.

Comments of John L. Festa, Ph.D., on behalf of the American Forest and Paper Association

Comment 1:

In response to OEHHA's request for comments on the subject draft technical support document, the American Forest & Paper Association (AF&PA) wishes to inform you of important new research on acrolein and acetaldehyde that supports biologically-based inhalation dose-response assessments for the two chemicals.

AF&PA is the national trade association of the forest, pulp, paper, paperboard and wood products industry. AF&PA's members include manufacturers of over 80 percent of the paper, wood and forest products produced in the United States.

I am providing herewith copies of five manuscripts, all accepted for publication in Inhalation Toxicology. Four manuscripts are on research performed at CIIT at the Hamner Institutes for Health Sciences. Another manuscript is on research performed by investigators from several institutions. The manuscripts are as follows:

(1) Nasal Uptake of Inhaled Acrolein in Rats.

(2) Respiratory Tract responses in Male Rats Following Sub-Chronic Acrolein Inhalation.

(3) Application of Physiological Computation Fluid Dynamics Models to Predict Interspecies Nasal Dosimetry of Inhaled Acrolein.

(4) PBPK Model for Evaluating the Impact of Aldehyde Dehydrogenase Polymorphisms on Comparative Rat and Human Nasal Tissue Acetaldehyde Dosimetry.

(5) Derivation of an Inhalation Reference Concentration Based Upon Olfactory Neuronal Loss in Male Rats Following Sub-Chronic Acetaldehyde Inhalation.

The above referenced studies in our view represent the best available science for determining Reference Exposure Levels (RELs: 8-hour and chronic) for acrolein and acetaldehyde, based on the detail of animal respiratory tract histopathology, and the development of physiological dosimetric models. These models reduce uncertainties and avoid the need for default interspecies dosimetric adjustments. We strongly recommend that OEHHA use these important new studies in deriving its RELs for acetaldehyde and acrolein.

Response:

At the time of release of the draft Technical Support Document for Non-Cancer Risk Assessment for public comment (November 2, 2007), which includes the appendix of Reference Exposure Level (REL) summaries, the aforementioned manuscripts on acetaldehyde had not been published. OEHHA has received and reviewed the newly published manuscripts: Dorman, D. C., M. F. Struve, et al. (2008). "Derivation of an inhalation reference concentration based upon olfactory neuronal loss in male rats following subchronic acetaldehyde inhalation." Inhal

*Toxicol **20**(3): 245-56; and Teeguarden, J. G., M. S. Bogdanffy, et al. (2008). "A PBPK model for evaluating the impact of aldehyde dehydrogenase polymorphisms on comparative rat and human nasal tissue acetaldehyde dosimetry." Inhal Toxicol **20**(4): 375-90. These are interesting papers and will contribute to the body of literature on acetaldehyde. We have made some additions and modifications to the acetaldehyde REL summary to reflect our consideration of these studies. First and foremost, this includes using the newly developed PBPK model for acetaldehyde in determining our 8-hour and chronic REL. We have used the dosimetric adjustment factor (DAF) provided in the Teeguarden et al., 2008 study of 1.36 to calculate a human equivalent concentration (HEC). In addition, although not included in the published manuscript (Dorman et al., 2008), OEHHA received the data tables for the manuscript from the author through a personal communication. Benchmark dose modeling was performed on the Dorman et al. (2008) data for incidence of degeneration of olfactory and respiratory epithelium. The data were found to be in good agreement with the classical study by Appelman et al., 1982; 1986 and used as supportive data for the calculation of the 8-hour and chronic RELs. Detailed descriptions of both studies have been added to the acetaldehyde REL summary.*

Comment 2:

Struve et al. (Nasal uptake of inhaled acrolein in rats), reported that the efficiency of acrolein uptake in naïve animals was dependent on the concentration of inspired acrolein, airflow rate, and duration of exposure, with increased uptake efficiency occurring with lower acrolein exposure concentrations. In acrolein pre-exposed animals, upper respiratory tract acrolein uptake efficiency was also dependent on the acrolein concentration used prior to the uptake exposure, with pre-exposed rats having higher uptake efficiency than their naïve counterparts. This suggests that chronic acrolein exposure may enhance its own uptake, an observation with bearing on the modeling described by Schroeter et al., as well as our estimation of the effects of chronic exposure.

In the Schroeter paper (Application of physiological computational fluid dynamics models to predict interspecies nasal dosimetry of inhaled acrolein) regarding the location and severity of lesions in the respiratory tract, it is reported:

> "The most severely affected site occurred along the lateral wall of Level II. Although this lesion occurred at a lower exposure concentration than the olfactory epithelial response, the rostral-caudal gradient in tissue doses observed in the present study demonstrated that olfactory epithelial responses occurred as lower tissue dose. This observation helped justify our use of the olfactory lesions as the critical effect in deriving a tissue-dose based NOAEL and applying this value to determine human health risks associated with inhaled acrolein."

Response:

The Schroeter study used the higher exposure concentration data to calculate the equivalent human tissue dose for their RfC calculation. There is no comparison with the expected tissue dose in the lateral wall of Level II at the lower NOAEL (0.2 ppm for respiratory epithelium lesions vs 0.6 ppm for olfactory neuronal loss). From the data presented it is not possible to derive a human-equivalent acrolein flux and dose for Level II. For regulatory purposes in

developing a REL, the lowest tissue dose at which the adverse effect occurs is not as important as the lowest applied concentration associated with an adverse effect. Thus, the NOAEL of 0.2 ppm is a more appropriate starting point to develop a REL (or RfC in Schroeter's case), than the 0.6 ppm concentration based on olfactory neuronal loss. This is important in light of the Struve et al. observation that the efficiency of acrolein uptake is higher at lower applied concentrations and declines with increasing concentration.

Schroeter et al. also assert

> *"This approach of selecting the region with the lowest flux value associated with less extensive injury should result in a conservative estimate of the local tissue dose needed to induce an adverse response. This flux value can therefore be considered a tissue dose-based NOAEL since it represents a more conservative approach than using the highest flux value at the NOAEL."*

We do not agree that the concentration of 0.6 ppm should represent a NOAEL vs a LOAEL. As noted above, given that the REL is derived from a concentration which has no effect, it is more appropriate to use the lower NOAEL for respiratory epithelium effects than it is to use the higher NOAEL for olfactory neuronal effects.

OEHHA wishes to thank AFPA for drawing our attention to these studies.

Comments of Scott Lutz, on behalf of the Bay Area Air Quality Management District.

Comment 1:

Some of the proposed procedures for REL development ensure adequate protection of children's health. Applying these revised procedures to develop 8-hour RELs will overestimate non-cancer risks for worker receptors. A REL protective of children is overly conservative for assessing risk to workers.

Response:

OEHHA agrees that this is a potential problem with the applicability of the 8-hour RELs to offsite workers, but is also aware that children are a possible or necessary component of the exposed population in other scenarios for which it has been suggested that 8-hour RELs should be applied. It must also be remembered that purely "occupational" adult-only scenarios still need to consider whether there is a daycare at the impacted workplace or the possibility of exposure to a pregnant worker and her fetus; so for developmental toxicants, there is still a concern that the REL is protective for in utero exposures.

OEHHA therefore will consider developing two separate 8-hour RELs, one with the child-specific models or uncertainty factors, and another using adult appropriate factors and models (but including fetal sensitivity for developmental toxicants) for use with adults only. Depending on the details of the individual derivation this might be a matter of changing the values of uncertainty factors or a more complex adjustment. Guidance on the circumstances in which these versions of the 8-hour REL should be applied will be given in the forthcoming revision of the Part IV (Exposure Assessment and Stochastic Analysis) technical support document.

Comment 2:

In order to ensure a more accurate assessment of the health impacts of intermittent exposure, non-cancer risks for receptors (e.g., workers and children) exposed on an intermittent basis should be addressed in the exposure assessment (e.g., by adjusting the receptor's exposure estimate or adjusting the air dispersion modeling); no adjustments should be made to the health values.

Response:

For simple cases and over modest timescale differences this approach is useful, and indeed that is what is recommended in the Part IV (Exposure Assessment and Stochastic Analysis) technical support document. However, there are many cases where a simple C x t correction to deal with exposure duration is insufficient, and it is not always clear whether acute or chronic toxic endpoints are the most critical at intermediate durations. This is one reason that OEHHA developed 8-hour RELs to address these situations and thereby reduce the complexity of choices and calculations necessary for the risk assessment, risk managers and facility owners.

Comment 3:

Nevertheless, if you intend to proceed with the 8-hour RELs, please describe the recommended exposure assessment and risk characterization procedures for use of the 8-hour RELs in calculating hazard quotients for different receptor populations (e.g., workers and children).

Response:

These will be addressed in the forthcoming revision of the Part IV (Exposure Assessment and Stochastic Analysis) technical support document.

Comment 4:

Since dose-based health values [cancer potency factors - (mg/kg-day)-1] are currently used to estimate cancer risks, dose-based RELs (mg/kg-day) should also be considered for use in estimating hazard quotients. This allows the consideration of receptor-specific breathing rates and body weights.

Response:

We consider this option potentially useful for certain toxicants, especially those which are bioaccumulative or cause cumulative chronic toxicity over extended exposure timeframes. Although we have not described this approach in the current document it is being actively considered for future use. It may be reflected in some forthcoming REL derivations and in the revision of the Part IV (Exposure Assessment and Stochastic Analysis) technical support document.

Comments of Ishrat S. Chaudhuri, Ph.D, DABT and Howard W. Balentine (ENSR), on behalf of the California Construction and Industrial Materials Association (CalCIMA).[1]

Comments on the General Methodology

Comment 1

OEHHA states that its preference is to use specific models, such as physiologically based pharmacokinetic (PBPK) modeling, when adequate data are available, rather than Uncertainty Factors (UFs). This approach is encouraged, since hopefully the resulting RELs would be based on scientific information and there would be less reliance on default UFs. However, because of inadequate data for most chemicals, OEHHA still proposes using the basic methodology of selecting one or more toxicity studies, developing a No Observed Adverse Effect Level (NOAEL), Benchmark Concentration (BMC), or Benchmark Dose (BMD) and dividing these by various UFs. Usually, the UFs are factors of 10 that are used to account for

- extrapolating from animals to humans (interspecies),
- accounting for sensitive individuals (intraspecies),
- using a subchronic study to develop a chronic value, and
- using a Lowest Observed Adverse Effect Level (LOAEL) rather than a NOAEL.

Despite the general lack of supporting documentation for the UFs that are currently used by OEHHA, USEPA and other agencies, OEHHA is proposing higher default UFs for a number of parameters. There is little hard scientific justification for the higher UFs. OEHHA is proposing changes in the default intraspecies and interspecies UF, and proposes to introduce an additional UF for database deficiencies. These UFs would be applied on a chemical-specific basis, so that not all chemicals will have the same UFs. However, for many chemicals, the net effect will be to lower the RELs based solely on the higher default UFs and without accompanying scientific justification for the higher UFs.

Response:

OEHHA appreciates the support of its proposal to use PBPK and other specific models when these are available or can be constructed. The commenter is correct in identifying the use of uncertainty factors as a frequent alternative due to lack of necessary data. OEHHA does not

[1] The report from ENSR containing these comments was also forwarded to OEHHA by Frank Sheets of the California Cement Manufacturers Environmental Coalition.

agree that there is a general lack of supporting documentation for the UFs currently in use. An early in depth review of UFs was published by Dourson and Stara in 1983 (Regulatory history and experimental support of uncertainty (safety) factors. Regul Toxicol Pharmacol. 3(3):224-38.). Additional data have accumulated since then. Some specific references are cited in the OEHHA document and in the responses to comments below. OEHHA considers that the proposed values for the various UFs reasonably represent the uncertainty inherent in the various defaults proposed, and cites various studies of data showing that the proposed ranges are consistent with those cases for which some data are available.

Comment 2: Intraspecies UF

The intraspecies UF to account for sensitive individuals (such as children) has previously been assigned a default value of 10. Investigators have proposed subdividing the intraspecies UF into toxicokinetic and toxicodynamic subfactors, with both of these factors having a default value of the square root of 10 (which is equal to approximately 3.2). OEHHA proposes a toxicokinetic subfactor of 10 to protect infants and neonates. Therefore, the total intraspecies UF becomes 30, rather than the current value of 10. Most agencies, including USEPA, believe that the UF of 10 for this factor is adequately protective. OEHHA (2007) states

> "Some studies suggested that the overall 10-fold factor was reasonable. Gillis et al. (1997) suggested, based on modeled intraspecies variability, that for chronic exposures, a 10-fold factor will protect the 85th percentile. On the other hand, more recent studies have indicated that a value higher than √10 should be considered for the pharmacokinetic component of the intraspecies uncertainty factor (UF_{H-k}), especially for substances that are bioactivated, since the enzymes involved in Phase I and Phase II reactions have shown pronounced polymorphism in many cases (Renwick and Lazarus, 1998; Hattis et al. 1999)."

However, most of the scientific studies do not suggest a specific UF. Charnley et al. (2005) investigated the current uses and level of protectiveness of UFs in determining safe doses for chemical exposures. They found that in larger populations close to 100% of the population (including children) is protected by using either a 10-fold UF for human variability or by using a 3.2-fold factor each for toxicokinetic and toxicodynamic variability. Burin and Saunders (1999) state that much of the evidence in the areas of pharmacodynamics and pharmacokinetics supports the routine use of an intraspecies UF in the range of 1 to 10 as being protective of greater than 99% of the human population. Therefore, several studies suggest that the UF of 10 for intraspecies sensitivity is highly protective. OEHHA does not provide specific scientific studies that would justify the use of a higher default toxicokinetic subfactor of 10, resulting in a total default intraspecies UF of 30.

It is noted that the Texas Commission on Environmental Quality (TCEQ) recently documented its methodology for developing Effects Screening Levels (ESLs; which are health-based air concentrations) and contracted with Toxicology Excellence for Risk Assessment (TERA) to conduct an independent, scientific peer review of the methodology. TERA is a nonprofit organization in Cincinnati, Ohio, that is internationally recognized for its peer reviews. The purpose of the peer review was to ensure that the TCEQ methodology for deriving ESLs meets the highest scientific standards. TERA convened an expert panel to discuss the methodology.

The panel members acknowledged that it is critical to consider the response of children since they may respond differently from adults. However, panel members also felt that an additional UF for children was not necessary and that USEPA's existing default UFs of 10 for intraspecies and interspecies extrapolation already adequately protect children. In its response report (Texas Commission on Environmental Quality, Responses to Peer Review Report, May 31, 2006), TCEQ responded that they agreed with the panel members that an additional UF for children was not necessary. The expert panel and TCEQ had access to the latest available toxicology information when determining that an additional UF was not necessary for the protection of children.

Therefore, available information indicates that a higher default intraspecies toxicokinetic UF of 10 should not be used. OEHHA's current default intraspecies toxicokinetic UF of √10 and toxicodynamic UF of √10 (resulting in a total intraspecies UF of 10) is adequately protective.

Response:

Several papers have been published, including those by Dourson, Charnley and colleagues at TERA, in which the authors have argued that the existing 10x default value for UF_H is adequate to protect children. OEHHA is of course familiar with these papers, but does not regard them as consistent with more recent work on the subject of uncertainty and variability in human response. For instance, Dourson et al. (2002) presented an extensive analysis defending the current UF_H as being adequate for all members of an exposed population including children and infants. In their Table 3 they present a list of U.S.EPA RfD's presumably indicating the adequacy of UF_H values of 10 or less over a wide range of chemicals. OEHHA's specific concern is that in the case of neonatal and young infants, the UF_{H-k} of √10 is probably inadequate to account for toxicokinetic differences by age, especially for inhalation exposure. A number of published analyses of human data and predictions from modeling indicate that an increase of the UF_{H-k} to 10 would be prudent in those cases where insufficient data are available. For example, the following studies support OEHHA's proposal:

8. *Renwick (1998) and Renwick et al. (2000) compared age-related differences in the pharmacokinetics of 36 drugs which are eliminated by different processes. Renwick et al. (2000) concluded that the main factor affected by age was the overall difference in clearance and the resulting elevated internal dose in neonates and children compared to adults. While these authors concluded that a UF_H value of 100 was not justified, they noted that an additional factor (>10) might be necessary in the case of a lack of developmental and reproductive toxicity data, inadequate data, or an irreversible toxic effect in neonates/young animals.*

9. *Dorne et al. (2001) evaluated the validity of the √10 UF_{H-k} in relation to CYP1A2 metabolism using published data for clearance (CL), AUC and peak plasma concentration (Cmax) for caffeine, theophylline, theobromine, paraxanthine, and R-warfarin in human volunteers. The authors identified subgroups for which the √10 would be inadequately protective including about half of pregnant women, nearly all neonates, and 13% of infants. These drugs were administered orally or parenterally.*

10. *Ginsberg et al. (2002) also evaluated child/adult pharmacokinetic differences in the drug*

literature. These authors identified about 100 chemicals with some pharmacokinetic data and analyzed a subset of 45. Multiple regression analysis was used to evaluate relationships between age groups and mean pharmacokinetic parameter (Cmax, half-life, AUC, volume of distribution, clearance). In general, for many chemicals, early life stages appeared different in terms of clearance, half-life, and volume of distribution. The overall study results indicate that premature and full-term neonates tended to have 3 to 9 times longer half-life than adults for the drugs studied. Like the earlier work of Renwick et al. (2000) and Dorne et al. (2001) the drugs studied were administered orally or parenterally, not by inhalation.

11. *Pelekis et al. (2001) used a PBPK model to derive adult and child pharmacokinetic UFs for a group of volatile organic compounds (VOCs). Adult models (50 and 90 kg) were compared with a 10kg child model. Simulations involved continuous exposure to 1 ppm VOC for 30 days. Modeled arterial, venous and tissue concentrations of the parent VOCs were used to calculate Adult/Child values. For the liver concentration metric the Adult/Child values were: styrene (0.033); xylene (0.037); trichloroethylene (0.061); dichloromethane (0.092); and chloroform (0.11). The model predictions indicate up to a 30-fold higher concentration of VOCs in child liver than adult liver. Unlike the drug studies above, this modeling study involves inhalation exposure of relevant environmental toxicants.*

12. *Jonsson and Johanson (2001) used a PBPK model of dichloromethane (DCM) to study the influence of metabolic polymorphism on cancer risk estimates. Exposure was by inhalation and metabolism by glutathione transferase theta (GSTT1) and mixed function oxidases (MFO) occurred in lung and liver. The model was fitted to published toxicokinetic data on 27 male volunteers exposed to 250-1000 ppm DCM. Excess cancer risk resulting from lifetime exposures to 1-1000 ppm DCM was estimated using Bayesian and Monte Carlo methods. The relevant dose metric was DNA-protein cross links (DPX) in liver derived from DCM metabolized via the GSTT1 pathway. Data on the frequencies of the three GSTT1 genotypes (0/0, +/0, +/+) in the Swedish population were used in the analysis. The results indicated a large interindividual variability in estimated risk, even within the two metabolizing groups (+/0, +/+). The results indicate that the UFHK of √10 for human PK variability may not be adequately protective for non-cancer endpoints, even among adults. One percent of the population would not be covered by a UFHK of 4.2-7.1 and 0.1 percent would not be covered by a UFHK of 7.3-14.5. While this study focuses on adults the results may apply even more strongly to infants and young children where inhalation may result in greater exposures per unit body weight, and metabolic systems, particularly MFO enzymes, are still under development.*

13. *Ginsberg et al. (2004) used PBPK modeling to evaluate the difference between neonates and adults in the metabolism of theophylline and caffeine. Both chemicals are metabolized by CYP1A2: caffeine to theophylline, theobromine, and paraxanthine; and theophylline to 3-methylxanthine, 1-methyluric acid, and 1,3-dimenthyluric acid. In neonates theophylline is "back" methylated to caffeine. Caffeine is cleared much more slowly in neonates than in adults (0.15 vs. 1.57 mL/kg-min, respectively) whereas theophylline is similarly cleared (0.35 vs. 0.86 mL/kg-min, respectively). The authors concluded that the extra back methylation path in neonates could largely account for the*

differences seen between neonates and adults. The results emphasize the importance of different metabolic pathways operating in neonates and infants during development.

14. *Gentry et al. (2003) evaluated the impact of pharmacokinetic differences on tissue dosimetry during pregnancy and lactation with PBPK modeling. Six chemicals were investigated: isopropanol, vinyl chloride, DCM, perchloroethylene, nicotine, and TCDD. Model predicted differences in dosimetry during pregnancy were largely the result of the development of metabolic pathways in the fetus or changes in tissue composition in mother and fetus. Generally, predicted blood concentrations were lower in the neonate during lactation than in the fetus during gestation. Predicted fetal/neonatal exposures vs. maternal exposures ranged from 2-fold greater (TCDD) to several orders of magnitude lower (isopropanol). The results of this study are in general agreement with earlier studies namely that the "age range of greatest concern is clearly the perinatal period. The most important factor appears to be the potential for decreased clearance of toxic chemicals … due to immature metabolic enzyme systems".*

15. *The recommendation of a default value of 10 for the kinetic component of the intraspecies uncertainty factor is also supported by our own analyses, summarized in Appendix E, in which pharmacokinetic modeling with adult and infant- or child-specific parameters for a number of inhaled toxicants was used to illustrate the likely range of age-related differences in internal dose for a given inhalation exposure to theses compounds.*

Comment 3: Interspecies UF

The interspecies UF is used to account for uncertainties in extrapolating from animals to humans, and assumes that humans are potentially more sensitive to the chemicals. Typically, USEPA and other agencies have used a default UF of 10 for animal to human extrapolation, which OEHHA is still planning to use for chemicals for which a Human Equivalent Concentration (HEC) cannot be derived. The HEC derivation is used to account for the toxicokinetic part of the difference between the species. In its derivation of chronic Reference Concentrations (RfC), USEPA has used the HEC and a UF of 3. OEHHA is recommending an additional UF of 2 when using the HEC procedure for adjusting RELs, resulting in a total interspecies UF of 6.32 (rather than the current 3.2). OEHHA provides little scientific evidence to suggest that the interspecies UF of 3 is not adequately protective when using the HEC procedure, and there is also little scientific justification for the additional factor of 2, resulting in an overall higher UF.

OEHHA should continue using OEHHA and USEPA's current default UF of 3 when using the HEC procedure.

Response:

OEHHA considers it inconsistent to ascribe the same level of uncertainty to an interspecies extrapolation using the HEC method (which addresses deposition, but fails to deal with absorption, systemic distribution, metabolism or excretion) as to a fully developed PBPK analysis which does address these considerations. U.S. EPA and various others have, since the original HEC publications, developed a number of more extensive treatments of intraspecies

extrapolation for inhalation exposures, which we consider preferable for those cases where they can be developed and supported by data.

Comment 4: Database Deficiency UF

OEHHA recommends an additional 3-fold UF to chemicals with substantial toxicological data gaps, including, but not limited to, developmental toxicity. This is an additional UF that OEHHA did not use in previous guidance. Again, there is little scientific justification for the specific value of, or even the need for, such a UF.

The database deficiency UF should only be used after considering the other UFs that will be used for a specific chemical. If UFs are used for all the other parameters, an additional UF for database deficiency should not be necessary.

Response:

A database deficiency UF is accepted risk assessment practice by most authorities, including U.S. EPA. OEHHA's previous guidance did not explicitly allow for database deficiencies. We now consider that OEHHA should include this factor in cases where it is justified. Each application of the database deficiency UF will be accompanied by a chemical-specific rationale.

Although this factor may be applied in a variety of different situations, the case where developmental toxicity data are lacking is of particular concern under that mandate of SB 25. OEHHA is thereby charged to determine if its health guidance values adequately protect infants and children. In some cases the database in animals does not include a developmental or reproductive toxicology study. In addition there may be no data on neonatal animals (or humans). In usual exposure studies animals are 4 to 8 weeks of age at the beginning of exposure. OEHHA does not agree that the other UFs necessarily cover such deficiencies in the database.

Comment 5: Cumulative UF

The net effect of the various higher default UFs is to increase the total cumulative UF, and lower the REL. OEHHA and other agencies' default assumption is that UFs are independent of each other, and may be combined through a multiplicative scheme. However, Calabrese and Gilbert (1993) argue that a lack of independence is seen in several cases, such as that between intraspecies and less-than-lifetime UFs, and could result in an error in double counting the UFs. For each individual chemical, it is important to consider the cumulative UF because the resulting REL may be unnecessarily low.

Response:

The changes in methods and default values for UFs proposed by OEHHA result in lower values for some RELs, and higher values for others. The effect of the proposals is case-specific, and cannot be predicted a priori.

The argument by Calabrese and Gilbert (1993) claims that multiple UFs can be regarded as probability distributions which can to some extent be "overlapped", thus reducing the overall range of UF needed. As OEHHA pointed out in more detail in the response to TERA, this analysis ignores the fact that these probability density functions are based mainly on uncertainty, not variability, and that individual sensitive populations represent independent response groups, not members of a single overall distribution (likely log-normal). On this basis there are no grounds for arguing against their independence or attempting to avoid "double counting". This is in any case not the argument used by U.S. EPA and other risk assessment experts to justify an overall limit on a cumulative UF: this was rather because if the indicated cumulative UF exceeded a certain value (typically 3000) that probably indicated that the overall supporting data were too poor to allow derivation of a reasonably reliable health protective level. This continues to be OEHHA's position on the issue, although we will consider larger uncertainty factors in exceptional cases.

Comments on Specific Chemicals:

1. Mercury

Comment 6

Mercury provides an example of a chemical where the OEHHA RELs are significantly lower than comparable values developed by other agencies, even though the same underlying toxicology studies were also used by the other agencies.

Table 1 compares the current and proposed OEHHA RELs for acute, 8-hour and chronic exposure times, as well as values developed by other agencies, such as ATSDR and USEPA.

Table 1. Comparison of Various Health Protective Air Concentration Values for Mercury ($\mu g/m^3$)

	Current OEHHA REL (1)	Proposed OEHHA REL (2)	ATSDR MRL (3)	USEPA RfC (4)	USEPA AEGL (5)
Acute	1.8	0.6	No value	No value	1700
8-hr	No value	0.06	No value	No value	No comparable value (6)
Chronic	0.09	0.03	0.2	0.3	No value

Notes:

(1) Current RELs listed in http://www.oehha.org/air/acute_rels/allAcRELs.html and http://www.oehha.org/air/chronic_rels/AllChrels.html .
(2) OEHHA (2007)
(3) Agency for Toxic Substances and Disease Registry (ATSDR) Minimal Risk Level (MRL) http://www.atsdr.cdc.gov/mrls/index.html
(4) USEPA Reference Concentration listed in the Integrated Risk Information System http://cfpub.epa.gov/ncea/iris/index.cfm
(5) USEPA Accidental Exposure Guideline Level (AEGL). AEGL 2 for 60 minutes - http://www.epa.gov/oppt/aegl/
(6) Even though 8-hr AEGLs have been developed, these are for single 8-hr exposures.

Response:

As noted in more detail below, there is no basis for comparison of the RELs to U.S. EPA's AEGL values. AEGLs (Acute Emergency Guideline Levels) are used to determine evacuation or shelter-in-place decisions in emergencies; they are not applicable to routine industrial releases. We are aware of the other values listed which were derived by U.S. EPA and ATSDR. While we certainly take account of their conclusions, the Air Toxics Hot Spots mandate requires that we make our own independent judgments in deriving the RELs, and we do not consider that these particular standards reflect the latest science, particularly in regard to providing special consideration of children's health in community exposure situations.

Acute REL

Comment 7

The proposed acute REL for mercury of 0.6 µg/m^3 was developed based on an inhalation study in pregnant rats. OEHHA used a UF of 10 for extrapolating from a Lowest Observed Adverse Effect Level (LOAEL) to a No Observed Adverse Effect Level (NOAEL), an interspecies UF of 30 (√10 for the toxicokinetic subfactor and 10 for the toxicodynamic subfactor), and an intraspecies UF of 10, resulting in a cumulative UF of 3000. This is a high total UF and results in a low acute REL. This value is 3-fold lower than the current acute REL of 1.8 µg/m^3, which uses an interspecies UF of 10.

There are no directly comparable values developed by ATSDR or USEPA. However, USEPA has developed Accidental Emergency Guidance Levels (AEGLs) to "*describe the risk to humans resulting from once-in-a-lifetime, or rare, exposure to airborne chemicals. The National Advisory Committee for AEGLs is developing these guidelines to help both national and local authorities, as well as private companies, deal with emergencies involving spills, or other catastrophic exposures*" (http://www.epa.gov/oppt/aegl). OEHHA (2007) states that these types of emergency guidelines are typically defined as predicted thresholds above which some level of adverse health effect is anticipated and for which standard margins of safety are not incorporated. Even though the AEGL values are not directly comparable, it is still worthwhile to note that the AEGL-2 60 minute value for mercury is 1700 µg/m^3, which is almost 3000-fold higher than the OEHHA acute REL. AEGL-2 values are based on a threshold for serious, long-lasting effects or an impaired ability to escape.

Response.

As the commentator recognizes, the AEGL-2 values are designed to prevent serious, long-lasting effects. They are by definition not based on the most sensitive endpoints and are designed to be life-protective, but not necessarily health-protective, in circumstances of single, accidental or rare exposures. In contrast, the acute REL is designed to prevent adverse health effects in the population at large, including sensitive subgroups, following infrequent but possibly repeated (no more than once every two weeks) exposures of one-hour duration. Thus the acute REL must be substantially lower than the AEGL.

Comment 8

USEPA did not have enough data to develop AEGL-1 values which are based on a threshold of discomfort. It is noteworthy that the acute REL is only 2-fold higher and 3-fold higher than USEPA and ATSDR chronic values, respectively. USEPA's Reference Concentration (RfC) is defined as "*An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. It can be derived from a NOAEL, LOAEL, or benchmark concentration, with uncertainty factors generally applied to reflect limitations of the data used*" (USEPA, 2008) It might be expected that a concentration protective of an acute exposure duration would be significantly higher compared to a concentration protective of daily exposure over a long period of time.

Response:

As noted in the previous comment, AEGL values generally are not comparable to the RELs, and comparison with these is inappropriate. The presumptive basis of an AEGL-1 (threshold of discomfort) is irrelevant to the problems of mercury toxicity. OEHHA agrees that the acute REL would be expected to be higher than the value for chronic exposure. This is, in fact, the case when the comparison is between proposed REL values rather than with USEPA values. The acute REL proposed by OEHHA is significantly higher (20x) than the proposed chronic REL (0.03 µg/m^3).

8-hr REL

Comment 9

The proposed 8-hour REL for mercury of 0.06 µg/m^3 was developed based on a human workplace study. A time-adjusted exposure concentration of 18 µg/m^3 was developed based on exposure for 8 hours per day and 5 days per week. OEHHA used a UF of 10 for extrapolating from a LOAEL to a NOAEL, and an intraspecies UF of 30 (√10 for the toxicokinetic subfactor and 10 for the toxicodynamic subfactor), resulting in a cumulative UF of 300. This UF is high given that the underlying toxicology study is a study in humans, and therefore does not include the uncertainties associated with extrapolating from an animal study.

Response:

The cumulative UF of 300 reflects OEHHA's concerns with the neurotoxicity of mercury especially in the context of exposures to fetuses, infants and children, whose nervous systems are developing. In the absence of a NOAEL, a LOAEL to NOAEL conversion UF of 10 was used because the endpoint of neurotoxicity is considered a severe effect. An intraspecies toxicokinetic UF of √10 was applied as a default value for inter-individual variability with the expectation that the kinetic parameters for inorganic mercury would not vary as much between children and adults as would the toxicodynamic parameters. For the toxicodynamic variability, a UF of 10 reflects the greater susceptibility of children's developing nervous systems to potentially long-lasting damage associated with early life exposure to inorganic mercury.

Comment 10

In its derivation of a chronic RfC for mercury, USEPA uses the same toxicology study but uses a 10-fold lower UF of 30 (USEPA, 2008). USEPA first developed a continuous exposure concentration of 9 μg/m^3. The UF of 30 consists of a factor of 10 for the protection of sensitive human subpopulations together with extrapolating from a LOAEL to a NOAEL; and a factor of 3 for the lack of developmental and reproductive studies. Dividing the concentration of 9 μg/m^3 by the UF of 30 results in an RfC of 0.3 μg/m^3.

In its derivation of a chronic inhalation Minimal Risk Level (MRL), ATSDR also uses the same toxicology study as OEHHA and USEPA, and uses a UF of 30 (ATSDR, 1999). An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. ATSDR developed a continuous exposure concentration of 6.2 μg/m^3. The UF of 30 consists of a factor of 10 for the protection of sensitive human subpopulations; and a factor of 3 for use of a minimal effect LOAEL. Dividing the concentration of 6.2 μg/m^3 by the UF of 30 results in an MRL of 0.2 μg/m^3. ATSDR states

> "Although this MRL is based on experimental data from an adult working population, there is no experimental or clinical evidence to suggest that it would not also be sufficiently protective of neurodevelopmental effects in developing embryos/fetuses and children, the most sensitive subgroups for metallic mercury toxicity."

It is also noteworthy that the 8-hour REL is lower than the USEPA and ATSDR chronic values, which consider continuous lifetime exposure.

Response:

While the ATSDR asserts that there is no evidence that their derived value would not be sufficiently protective of neurodevelopmental effects, OEHHA considers that the similarities in the toxic effects of elemental mercury and methylmercury (see response below), for which ample data exist, indicate a profound differential sensitivity of the developing nervous system to mercury compounds, and therefore warrant the greater protection afforded by higher UFs. In addition, the 8 hour REL is meant to cover repeated daily 8-hour exposures, not just occasional single 8-hour exposures.

Chronic REL

Comment 11

The proposed chronic REL for mercury of 0.03 μg/m^3 was developed based on the same human workplace study on which the 8-hr REL is based. A time-adjusted exposure concentration of 8.9 μg/m^3 was developed to consider continuous exposure. OEHHA used a UF of 10 for extrapolating from a LOAEL to a NOAEL, and an intraspecies UF of 30 (√10 for the toxicokinetic subfactor and 10 for the toxicodynamic subfactor), resulting in a cumulative UF of 300.

As noted in the previous section, both USEPA and ATSDR used the same study but a 10-fold lower UF of 30 to derive chronic levels that are 10-fold higher than the proposed OEHHA REL. OEHHA (2007) states that the default intraspecies UF may be increased to 10 for the toxicokinetic subfactor, but that the toxicodynamic subfactor would remain at √10. OEHHA does not provide enough justification for increasing the toxicodynamic subfactor for mercury to 10.

There appears to be general consensus amongst various regulatory agencies on the toxicology study used to develop a chronic inhalation value for mercury vapor. Both USEPA and ATSDR state that the UF of 30 is sufficiently protective of children and other sensitive groups. OEHHA's total UF of 300 is not warranted given that the toxicology study considers exposure to humans.

Response:

As indicated in the section on chronic effects on children, there is a substantial body of literature indicating the children are more sensitive than adults to the adverse neurological effects of methylmercury (Choi, 1989; Harada, 1995; Grandjean et al., 1999). Part of OEHHA's concern with elemental mercury is by analogy to methylmercury. Both elemental and methylmercury are lipophilic and readily cross membranes including those of the placenta and blood-brain barrier. Intracellularly, both are converted to the mercuric ion that is not as membrane permeant as the parent species. In adults the mercuric ion tends to accumulate in the kidneys, while it becomes more widely distributed in the neonate with relatively more concentrating in the brain than in adults (NAS, 2000). Since cells of the developing nervous system of fetuses and neonates are rapidly dividing and differentiating, they are much more susceptible to mercury toxicity. Damage to the CNS during development is thus likely to have permanent effects. This is the main reason for the increased toxicodynamic UF. We will include this information in the section describing the chronic REL derivation to clarify our position.

Comparison of RELs to Ambient Air Concentrations

Comment 12

One practical problem with developing excessively low RELs is that the RELs could be similar to, or lower than, ambient air concentrations. ASTDR (1999) states that ambient air concentrations of mercury have been reported to average approximately 0.01 – 0.02 μg/m^3, with higher concentrations in industrialized areas. These concentrations are close to the proposed chronic REL of 0.03 μg/m^3. If there are monitoring requirements for facilities, then it might be difficult to distinguish between facility sources and ambient levels at concentrations close to the chronic REL.

Response:

The question of ambient levels is fundamentally irrelevant to the derivation of a REL. The relation between the REL, the extent of an emission from a particular facility, and the ambient levels in the vicinity of that facility are matters to be considered at the risk management stage. The REL is designed to be health-protective irrespective of ambient levels and, as a result, may

be lower than ambient levels in some areas for some substances. While acknowledging that the proposed chronic REL is close to ambient levels in some areas, it is important also to recognize that ambient levels comprise both naturally emitted mercury (of which there is very little in most areas) and mercury released from anthropogenic sources. The latter source may be amenable to reduction. In addition, even naturally generated ambient levels of a substance are not necessarily without adverse health effects.

2. Manganese

Comment 13: Impact of Uncertainty Factors

For manganese, both USEPA (2008) and ATSDR (2000) used the same toxicology study to derive a chronic REL and MRL of 0.05 µg/m^3 and 0.04 µg/m^3 respectively, both of which are higher than the OEHHA chronic REL of 0.03 µg/m^3. The main difference is that OEHHA used a cumulative UF of 2000, whereas USEPA used a cumulative UF of 1000 and ATSDR used a cumulative UF of 500. OEHHA used an intraspecies UF of 100 (10 for toxicokinetics and 10 for toxicodynamics). OEHHA (2007) recommends a default intraspecies UF for toxicokinetics of 10, and √10 for toxicodynamics (which would result in a total intraspecies UF of approximately 30). OEHHA does not provide compelling scientific justification for also including a UF of 10 for toxicodynamics in the case of manganese, resulting in a total intraspecies UF of 100.

The results for mercury and manganese show that the net effect of the various higher default UFs is to increase the total cumulative UF, and lower the REL. Most regulatory agencies believe that the existing UFs are sufficiently protective of sensitive individuals, such as infants. OEHHA provides little hard scientific justification for the higher UFs.

Response:

As mentioned above regarding the UFs used with mercury, OEHHA is concerned that there is convincing evidence of a differential sensitivity of the developing nervous system to manganese. Both adult and developmental neurotoxicity have been demonstrated for manganese. However, because there is much less information regarding the toxicity of inhaled manganese in the young, OEHHA chose to use higher UFs precisely to reflect this uncertainty. We have received a large number of comments on manganese, and several new studies have appeared recently, so OEHHA is revising the manganese RELs to reflect this new information. OEHHA has obtained the data for individuals from the Roels et al. (1992) study and used these to conduct a BMD analysis to generate a $BMDL_{05}$ as a point of departure for the REL determination. This has eliminated the LOAEL to NOAEL UF of 6, thus lowering the cumulative UF to 300. The other UFs remain the same and the resulting proposed chronic REL is 0.11 µg/m^3.

Comment 14: Essential Nutrient Status of Manganese

Another important issue for manganese is that it is an essential nutrient, and the REL needs to account for the amount of manganese that is required by our bodies for overall health. The proposed chronic REL is a small fraction of the permissible amount from the diet. The low REL is not justified in light of the fact that our bodies require a higher amount of manganese to function.

Response:

OEHHA recognizes the essentiality of manganese in the diet. The important point is that the manganese taken into the body to be used in essential metabolic functions enters via the oral route as part of the diet, not via inhalation. This difference in routes is critical as inhaled manganese has more direct access to the brain via olfactory nerves, and to the brain and other organs via uptake from the lungs into the blood without first pass elimination in the liver. In addition, manganese is much more efficiently taken up from the lungs than from the digestive tract. Manganese levels resulting from absorption from the intestinal tract are well regulated in adults by an entero-hepatic circuit, a regulatory mechanism that appears to be less effective in the young, and missing entirely in young infants. In adults, 2-5% of manganese ingested with the diet is retained in the body (Andersen et al., 1999), while 20 to 41% may be retained by formula and breast-fed infants, respectively (Dorner et al., 1989). This difference in absorption is compounded by the fact that in the very young, the difference in manganese levels that are appropriate and those that are toxic is very much smaller than in adults. Thus, it is much easier to exceed safe levels in neonates and small children than in adults.

Comment 15: Comparison of RELs to Ambient Air Concentrations

ATSDR (2000) reports that annual averages of manganese in urban and rural areas without significant manganese pollution are in the range of 0.01 – 0.07 μg/m^3. These concentrations encompass the proposed 8-hour and chronic RELs for manganese (0.05 and 0.03 μg/m^3, respectively).

Response:

The purpose of the REL is to define a level which can reasonably be regarded as safe. Thus, the REL can serve as an important indicator that ambient background exposures raise public health concerns or not. It is reassuring that there are only select cases where the background exposure to a toxicant of interest approach or exceed a REL; conversely, it is disturbing that there are a few cases where ambient exposures have been sufficiently well studied to be an indicator of a safe level. The purpose of the REL under the Hot Spots program is to assist risk managers in determining what would be reasonable as an incremental emission by a facility. Any consideration of the existing background either locally or in general would be a matter for the risk manager to evaluate. [Staff also notes that many National Ambient Air Quality Standards, which are legal exposure levels for a special set of toxic air pollutants, are near their background levels.]

3. Arsenic

Basis for 8-hr and Chronic RELs

Comment 16:

The 8-hr and chronic RELs for arsenic (0.015 μg/m^3) are both based on a study that has serious drawbacks to being the basis for an inhalation reference concentration. The RELs are based on a study involving drinking water exposure to arsenic of 10-year old children in Bangladesh

(Wasserman et al. 2004). The study evaluated intellectual function in children, and determined that arsenic in drinking water was associated with reduced intellectual function in a dose-dependent manner. OEHHA used this study to develop the 8-hr and chronic RELs which evaluate inhalation exposure. There are many uncertainties associated with using an oral study to develop an inhalation value. The drinking water study itself is likely to have many uncertainties related to the arsenic doses actually received by the children. The children's health is likely to be compromised due to poor nutrition and contamination of water by other metals, such as manganese. It is not clear that this study could be related directly to US children who have different nutrition. OEHHA had to make various assumptions in order to convert a drinking water intake level to an inhalation reference concentration. The assumptions included a water intake of 1L/day, complete gastric absorption, inhalation rate of 10 m^3/day and 50% inhalation absorption. While there may be some basis to these assumptions, the combination of all the assumptions results in a very uncertain value.

OEHHA does not provide any documentation on its assumption of 50% absorption through the inhalation route. A study by Beck et al. (2002) suggests that arsenic inhalation has a negligible impact on body burden of inorganic arsenic until air levels are significantly elevated. In this study, rabbits were exposed to one of four levels of arsenic trioxide in air for 8 h/day, 7 days/week, for 8 weeks (0.05, 0.1, 0.22, or 1.1 mg/m^3). Plasma levels of inorganic arsenic, monomethylarsonic acid (MMA), and dimethylarsinic acid (DMA) were measured following the last exposure. Statistically significant increases in mean inorganic arsenic levels in plasma were observed only in male rabbits exposed to 0.22 mg/m^3, and in both males and females exposed to 1.1 mg/m^3. Mean inorganic arsenic levels in plasma in males and females exposed to 0.05 and 0.1 mg/m^3, and females exposed to 0.22 mg/m^3, were not significantly elevated compared to controls. Based on plasma measurements of inorganic arsenic, the two lowest exposure levels in this study (0.05 and 0.1 mg/m^3) are indistinguishable from background. These results suggest that 50% absorption through the inhalation route may be an overestimate. It is also important to note that the chronic REL of 0.015 µg/m^3 is a tiny fraction (0.015%) of the concentration of 100 µg/m^3 at which no elevated plasma levels were seen in rabbits.

OEHHA used USEPA exposure assumptions to describe exposures in Bangladeshi children, and assumed that the health effects of drinking water exposure are equivalent to inhalation exposure. OEHHA also used an intraspecies UF of 10 to derive the REL. This UF is likely to be high given that the exposed population is children, who are also likely to be in poorer health than US children. All of these factors indicate that the 8-hr and chronic RELs for arsenic based on this study are likely to be unrealistically low.

Response:

The commentator is concerned that using an oral study to develop an inhalation REL is problematic, that the children in the study are not comparable to US children, that there is uncertainty regarding absorption following inhalation of arsenic, and that the intraspecies UF of 10 is too high. OEHHA believes that oral studies are relevant to assess human inhalation risk. Since airborne arsenic is likely to be associated with the inhalation of particles, absorption is very likely to involve oral as well as inhalation uptake following arsenic particle deposition in the respiratory tract. There was no suitable inhalation study to evaluate this endpoint. Due to widespread contamination of drinking water supplies with inorganic arsenic all of the most

relevant human epidemiology addresses exposures from this source. OEHHA acknowledges that epidemiological studies often lack the detailed dosimetry data of controlled animal experiments. However, with respect to arsenic exposure and human developmental neurotoxicity there are now a number of studies reviewed in the TSD that support OEHHA's selection of it as the key endpoint for noncancer risk assessment. Although we selected the Wasserman et al. (2004) study as the basis of the 8-hour and chronic RELs, it is closely supported by the Tsai et al. (2003) study with different cognitive endpoints.

OEHHA has often used 50% as a default for respiratory uptake where chemical specific data are lacking. As noted above human inhalation of arsenic is very likely to involve particle inhalation. Particle deposition and uptake depend on a number of factors principally particle size. For particles with a mean diameter of 1µm and breathing 0.09 to 0.31 m^3/hour the ICRP (Human Respiratory Tract Model for Radiological Protection, ICRP Publication 66, 1994) predicts total deposition of 42 to 54% for children three months to ten years of age, respectively. OEHHA believes that 50% is an appropriate assumption in view of uncertainties regarding particle size distribution, dissolution rates, efficiency of mechanical removal and ingestion of swallowed particles.

Comment 17:

It is also noted that Wasserman et al. (2006) conducted a similar study for manganese evaluating the exposure of children in Bangladesh to manganese in drinking water, and also found a dose-dependent correlation with intellectual function. Although OEHHA reviewed this study, it did not make use of this study to develop an REL for manganese. Instead, the chronic REL for manganese is based on a workplace inhalation study. OEHHA should have tried to use an inhalation study to develop the REL for arsenic.

Response:

Although inhalation studies are generally preferred for developing inhalation RELs, in the case of arsenic OEHHA believes that the neurodevelopmental endpoints studied by Wasserman et al. (2004) and Tsai et al. (2003) and the study subjects evaluated (i.e., children) trump the route of exposure. In our view the occupational study of Blom et al. (1985) was not suitable for quantitative (Benchmark Concentration) analysis. This study of 47 arsenic-exposed copper smelter workers and 50 industrial worker controls had only a single exposure or dose group and was therefore inadequate for dose response evaluation. Furthermore the single exposure was rather ill-defined ranging from 500 µgAs/m^3 in 1940-1975 and 50 µgAs/m^3 thereafter.

Comment 18:

OEHHA (2007) has also conducted similar calculations using other drinking water studies in children (Siripitayakunkit et al. 1999; Siripitayakunkit et al. 2001, Mazumder et al. 1998 and Tsai et al. 2003). The chronic RELs derived by OEHHA using these other studies are higher, ranging from 0.05 to 1.6 µg/m^3 (Table 8.3.1 in Appendix D; OEHHA, 2007). All of these chronic RELs also include an intraspecies UF of 10, which appears unnecessary since these studies were also conducted in children. OEHHA states that the geometric mean of the three studies evaluating a cognitive endpoint is 0.053 µg/m^3. Given the uncertainties inherent in any

one study, it is not clear why OEHHA just used the results of the one study resulting in the lowest value of 0.015 µg/m^3. When developing dose-response values, USEPA often uses the geometric mean of several studies. For example, the inhalation unit risk factor for arsenic (which evaluates carcinogenic effects) is based on a geometric mean of several studies (USEPA, 2008). In selecting the results of one study, OEHHA is not conforming to its own guidance which states a preference for using the results from various studies and calculating benchmark doses (OEHHA, 2007).

Response:

As noted in previous responses, OEHHA chose the Wasserman et al. (2004) study as the basis of the 8-hour and chronic RELs supported by the Tsai et al. (2003) study. OEHHA believes that these studies are stronger for the neurodevelopmental toxicity endpoint than the studies of Siripitayakunkit et al. (1999, 2001). The study of skin lesions by Mazumder et al. (1998) was included for comparison but is not considered as serious an endpoint for children's risk assessment. In some previous assessments we have used geometric means to address specific study uncertainties, but here we decided to pick a single best study with appropriate supporting studies. OEHHA uses a geometric mean when the studies are considered to be of equal merit, or combines the sexes when they are equally sensitive. When this is not the case the guidelines recommend use of the study with the most sensitive site, sex, and species. OEHHA chose to use the most health protective value of the most serious toxic effect seen in children. For benchmark dose analysis the data need to be amenable.

The uncertainty factor of 10 is health protective and reflects our continuing concern about these neurotoxic effects in children as well as uncertainty with respect to metabolism and mode of action. As noted in the REL summary, the tenfold factor is designed to include additional uncertainty with regard to the route-to-route extrapolation (drinking water to inhalation), given the complexity of arsenic uptake, distribution and metabolism. OEHHA may use an intraspecies UF of less than 10 when sensitive individuals such as children were exposed in a key study, but this is generally in the context of a study with exposure via the route of concern. Also, the intraspecies toxicokinetic UF of 10 proposed in the current draft guidance is intended to protect not only children but infants and neonates. These are not included in the key study population since they are not direct consumers of drinking water (at least in the countries where the studies were conducted, where use of formula is uncommon).

If more data become available concerning the pharmacokinetics, mode of action and persistence/reversibility of these effects we will revise the assessment as needed.

Comment 19: Concentrations Developed by Other Agencies

USEPA or ATSDR have not derived inhalation reference concentrations for arsenic based on noncancer effects because of a lack of suitable studies. However, the Netherlands' National Institute of Public Health and the Environment (RIVM, 2001) has developed a Tolerable Concentration in Air (TCA) for arsenic of 1 µg/m^3 that is protective of both cancer and noncancer effects. RIVM notes that lung cancer occurs in humans at concentrations greater than 10 µg/m^3. However, RIVM indicates that the mechanism for tumors is not directly genotoxic, so a threshold exists for this effect. Therefore, RIVM elected to call the value a TCA, not a cancer

risk value, and applied an uncertainty factor of 10 to account for intrahuman variability. This value is two orders of magnitude higher than the proposed chronic REL of 0.015 µg/m^3.

Response:

OEHHA does not concur with RIVM's interpretation of the carcinogenicity data. As noted in the Air Toxics Hot Spots Technical Support Document Describing Available Cancer Potency Factors, we find no evidence of a threshold for arsenic carcinogenicity, and derive a cancer slope factor to describe the dose response for this effect. In our view inorganic arsenic exposure by the oral or inhalation routes presents a serious risk of toxic effects (both carcinogenicity and neurotoxicity) in children and adults. The risks of chronic arsenic exposure in adults were largely ignored or severely underestimated for decades, and significant additional risks to children have only recently been appreciated. Regardless of the actions or criteria of other health agencies, we must comply with our own mandates and scientific review process.

Comment 20: Comparison of RELs to Ambient Air Concentrations

ATSDR (2007) states that mean levels of arsenic in ambient air in the United States have been reported to range from <0.001 to 0.003 µg/m^3 in remote areas and from 0.02 to 0.03 µg/m^3 in urban areas. The background concentrations in urban areas are close to the chronic REL for arsenic.

Response:

As OEHHA staff indicated above in the response to Comment 12 about mercury and Comment 15 about manganese, the value of the background concentration is of no relevance to the value of the REL. Any consideration of the existing background either locally or in general would be a matter for the risk manager to evaluate.

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Comments prepared by Exponent on behalf of various interested parties[1].

Comment 1: Advances Offered by the Proposed Revisions

There are several elements of these draft guidance for which we concur and consider consistent with current technological advances and state of the science for children's heath. Of particular note:

1. PBPK analysis, when feasible of the most sensitive age group, allows inclusion of all relevant data, and provides a more accurate method to develop RELs than the application of UFs. As recognized by OEHHA, the use of UFs is an imprecise method for setting RELs. Although PBPK models are not available for all chemicals for which RELs will be determined, the use of these models and other toxicokinetic information should reduce the need for UFs.

2. The use of BMC_{05} for modeling developmental toxicity data is conservative and adequately protective of the sensitive subpopulations as indicated in the technical support documents. The selection of other response rates such as 1% results in unreasonable and inappropriate application of benchmark dose approach for risk assessment.

3. Generally, the approaches recommended for revision are consistent with advancements made by the U.S. Environmental Protection Agency for the development of Reference Concentrations and Doses (RfCs and RfDs), and concurrence with federal guidelines provides an important benchmark for these revisions.

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[1] These comments were prepared by Exponent acting as consultants for
Tim Shestek, American Chemistry Council (ACC)
Mike Rogge, California Manufacturers & Technology Association (CMTA)
Rob Neenan, California League of Food Processors (CLFP)
Chris Conkling, USS Posco Industries (UPI)
Cathy Reheis-Boyd, Western State Petroleum Association (WSPA)
Cynthia Cory, California Farm Bureau Federation (FB)
Frank Sheets, California Cement Manufacturers Environmental Coalition (CCMEC)
Patti Krebs, Industrial Environmental Association (IEA)
Jason Schmelzer, California Chamber of Commerce
Pamela Williams, California Retailers Association (CRA)
John Ulrich, Chemical Industry Council of California (CICC)
Jed Mandel, Engine Manufacturers Association (EMA)
Jay McKeeman, California Independent Oil Marketers Association (CIOMA)
John Marrs, Surface Technology Association (STA)
Bill Wiggins, Metal Finishing Association of Southern California, Inc. (MFASC)

Response:

OEHHA thanks Exponent for their thoughtful analysis, and appreciates these supportive comments. We note in response to the first point that, although as we propose in the draft Technical Support Document it is generally desirable to use PBPK modeling when possible, there are a number of limitations to this in practice. Some of these are discussed in response to other comments (see, inter alia*, our response to NRDC comment number 4). OEHHA's analysis in the document also makes clear that while we find that the lower 95% confidence limit on BMC_{05} is a suitable benchmark for most quantal responses in animal toxicity studies, there may be cases where a different benchmark is preferred, especially for continuous data or epidemiological studies. Selection of a different benchmark may require use of modified uncertainty factors where sample size increases confidence in the dose response at lower levels. Finally, although the primary objective in this revision was to comply with Californian legislative mandates and to incorporate the latest scientific advances, we are pleased to note that we are to a considerable extent consistent with current U.S. EPA guidance, and we would like to acknowledge the extensive and helpful discussions we have had with our colleagues at the Federal level over the last several years.*

Further Discussion of the Proposed Revisions:

To facilitate implementation of the tools provided by this guidance, expanded discussion of the following points is requested:

Comment 2:

Potential for methodological inconsistencies may arise from efforts to harmonize the methodologies for acute, eight-hour and chronic RELs. Explicit delineation of procedures taken to harmonize the derivation process of RELs for different exposure durations would strengthen the scientific basis of the technical support document. For example, 8-hour RELs are defined as concentrations below which health effects are not likely to occur in the general human population with intermittent exposures of 8 hours per day, 5 days per week (OEHHA 2007 page 84). However, on page 2 the guidance states that 8-hour RELs are protective of exposures that could occur daily. The guidance should be clarified as to whether these guidance levels are for 5 day per week exposures or daily exposures.

Further, the technical support document states that chronic RELs may underestimate the noncancer risk when facility operations, occurring only 8- hours per day correspond with 8-hour per day exposures to non-residential populations (OEHHA 2007 page 84). It is noted that this is problematic in AB2588 risk assessment applications. However, in these situations the chronic RELs do not underestimate risk; rather exposure is underestimated. It is not appropriate to develop new approaches to calculate more conservative 8-hour RELs to correct for possible underestimates in exposure. In AB2588 risk assessments, 8-hour RELs can be compared to model estimated 8-hour airborne concentrations that correspond to when emissions and exposure actually occur. Thus, the exposure assessment should be improved, and toxicity criteria should not be amended in an attempt to address this potential problem.

A time adjustment factor to account for 5 days per week should not be applied for chemicals posing chronic toxicity when the point of departure is derived from occupational LOAELs or NOAELs. As defined on page 84, 8-hour RELs are protective of 5 day per week exposures and the occupational exposures from which the LOAEL or NOAEL is derived is for exposures that occur 5 days per week; thus this correction is redundant and should not be incorporated. The stated technical basis for including the correction for some chemicals (e.g., mercury and manganese) is that the chemicals are slowly cleared from the body and that bioconcentration in body tissues occurs. While this is a valid observation, it should be considered that bioconcentration also occurs among the workers from which the LOAEL (or NOAEL) is derived and is inherently accounted for in the LOAEL. Thus, it is not appropriate to add this additional time adjustment factor for manganese, mercury or other similar chemicals for which 8-hour RELs are developed from occupational exposures.

Response:

OEHHA thanks the commenter for pointing out the inconsistency in our description of the 8 hr REL and has revised the draft TSD to clarify the description of the applicability of 8-hour RELs. However, it should be noted that not all 8-hour RELs deal with long-term effects, or use 8-h per day, 5 days a week assumptions, and the applicability of these considerations is therefore different according to the particular case being considered. It is not intended that applications of 8-hour RELs will be confined to five days per week. Many facilities operate seven days a week, and the exposed individuals include categories besides workers on a standard daily shift. This means that it cannot simply be assumed that bioconcentration issues are covered by the timing of exposures in the critical study where this happens to be of an occupational exposure. Since (as noted elsewhere) OEHHA intends to develop both child- and adult-specific version of the 8-hour REL, more complex adjustments may be required in some cases to reflect different uptake and kinetic properties, as well as intrinsic sensitivities, for infants, children and adults. Further discussion of the 8-hour RELs and associated exposure assessment procedures will appear in a forthcoming revision to the technical support document dealing with exposure assessment and stochastic risk assessment (currently the Part IV TSD).

Comment 3:

The potential exists for unnecessarily high cumulative uncertainty factors when additional intraspecies UF and database deficiencies UF are applied to account for increased susceptibility in sensitive subpopulations. It is important to recognize that the point of departure (LOAEL or NOAEL) already accounts for more sensitive individuals (i.e., the lower bound of the response curve) and a 10-fold factor for intraspecies variability generally offers adequate protection, as discussed in detail in Dourson et al. (2002).

As noted in the Recommendations Chapter of the USEPA *Review of Reference Dose and Reference Concentration Processes* (USEPA 2002, page 5-5), it is imperative that justification for individual UFs be provided because rigid application of UFs could lead to an illogical set of reference values. The exact value of the UF chosen should depend on the quality of the studies available, the extent of the database, and scientific judgment. Sound scientific judgment should be used in the application of UFs to derive reference values that are applied to the value chosen for the point of departure derived from the available database (BMDL, NOAEL, or LOAEL).

Finally, it should be noted that EPA's Technical Panel found that prior work addressing sensitive subpopulations including children and the elderly (Renwick and Lazarus, 1998; Renwick 1998; Abdel-Mageed et al., 2001) suggests that the overall 10- fold intraspecies UF is "sufficient in most cases" and that with chemical specific data, a lower value may also be appropriate (USEPA 2002, Page 4- 43). Thus, OEHHA's revision to use a default UF_H of 30 for chemicals causing systemic toxicity may be overly conservative and should be examined by scientists with expertise in children's health on a chemical-by-chemical basis.

Response:

OEHHA agrees that the values of uncertainty factors used in chemical-specific risk assessments should be justified in the REL summaries for each individual chemical based on the quality and extent of the database (which we have done in the examples provided), and that scientific judgment is necessary. It is a basic principle of these guidelines, expressed at various points throughout the narrative, that the default values are used in the absence of sufficient information, and are replaced with values or procedures based on actual chemical- or population-specific data where these are available. However, it has also been necessary to define suitable defaults where such specific data are lacking. OEHHA has determined that the value of 10 for $UF_{H\text{-}k}$ is the most appropriate default to reflect the toxicokinetic differences between infants, children, and adults, as well as the variability among adults. This conclusion is based both on our own analyses (summarized in Appendix E) and on extensive scientific publications. The earlier publications cited in the comment are less persuasive than the larger and more recent literature suggesting that a default factor of 10 is not sufficient to protect infants and children. For example, the following studies support OEHHA's proposal:

16. *Renwick (1998) and Renwick et al. (2000) compared age-related differences in the pharmacokinetics of 36 drugs which are eliminated by different processes. Renwick et al. (2000) concluded that the main factor affected by age was the overall difference in clearance and the resulting elevated internal dose in neonates and children compared to adults. While these authors concluded that a UF_H value of 100 was not justified, they noted that an additional factor (>10) might be necessary in the case of a lack of developmental and reproductive toxicity data, inadequate data, or an irreversible toxic effect in neonates/young animals.*

17. *Dorne et al. (2001) evaluated the validity of the $\sqrt{10}$ UF_{HK} in relation to CYP1A2 metabolism using published data for clearance (CL), AUC and peak plasma concentration (Cmax) for caffeine, theophylline, theobromine, paraxanthine, and R-warfarin in human volunteers. The authors identified subgroups for which the $\sqrt{10}$ would be inadequately protective including about half of pregnant women, nearly all neonates, and 13% of infants. These drugs were administered orally or parenterally.*

18. *Ginsberg et al. (2002) also evaluated child/adult pharmacokinetic differences in the drug literature. These authors identified about 100 chemicals with some pharmacokinetic data and analyzed a subset of 45. Multiple regression analysis was used to evaluate relationships between age groups and mean pharmacokinetic parameter (Cmax, half-life, AUC, volume of distribution, clearance). In general, for many chemicals, early life stages appeared different in terms of clearance, half-life, and volume of distribution. The*

overall study results indicate that premature and full-term neonates tended to have 3 to 9 times longer half-life than adults for the drugs studied. Like the earlier work of Renwick et al. (2000) and Dorne et al. (2001) the drugs studied were administered orally or parenterally, not by inhalation.

19. *Pelekis et al. (2001) used a PBPK model to derive adult and child pharmacokinetic UFs for a group of volatile organic compounds (VOCs). Adult models (50 and 90 kg) were compared with a 10kg child model. Simulations involved continuous exposure to 1 ppm VOC for 30 days. Arterial, venous and tissue concentrations of the parent VOCs were used to calculate Adult/Child values. For the Liver concentration metric the Adult/Child values were: styrene (0.033); xylene (0.037); trichloroethylene (0.061); dichloromethane (0.092); and chloroform (0.11). The model predictions indicate up to a 30-fold higher concentration of VOCs in child liver than adult liver. Unlike the drug studies above this modeling study involves inhalation exposure of relevant environmental toxicants.*

20. *Jonsson and Johanson (2001) used a PBPK model of dichloromethane (DCM) to study the influence of metabolic polymorphism on cancer risk estimates. Exposure was by inhalation and metabolism by glutathione transferase theta (GSTT1) and mixed function oxidases (MFO) occurred in lung and liver. The model was fitted to published toxicokinetic data on 27 male volunteers exposed to 250-1000 ppm DCM. Excess cancer risk resulting from lifetime exposures to 1-1000 ppm DCM was estimated using Bayesian and Monte Carlo methods. The relevant dose metric was DNA-protein cross links (DPX) in liver derived from DCM metabolized via the GSTT1 pathway. Data on the frequencies of the three GSTT1 genotypes (0/0, +/0, +/+) in the Swedish population were used in the analysis. The results indicated a large interindividual variability in estimated risk, even within the two metabolizing groups (+/0, +/+). The results indicate that the UF_{HK} of $\sqrt{10}$ for human PK variability may not be adequately protective for non-cancer endpoints. One percent of the population would not be covered by a UF_{HK} of 4.2-7.1 and 0.1 percent would not be covered by a UF_{HK} of 7.3-14.5. While this study focuses on adults the results may apply even more strongly to infants and young children where inhalation may result in greater exposures per unit body weight, and metabolic systems, particularly MFO enzymes, are still under development.*

21. *Ginsberg et al. (2004) used PBPK modeling to evaluate the difference between neonates and adults in the metabolism of theophylline and caffeine. Both chemicals are metabolized by CYP1A2: caffeine to theophylline, theobromine, and paraxanthine; and theophylline to 3-methylxanthine, 1-methyluric acid, and 1,3-dimenthyluric acid. In neonates theophylline is "back" methylated to caffeine. Caffeine is cleared much more slowly in neonates than in adults (0.15 vs. 1.57 mL/kg-min, respectively) whereas theophylline is similarly cleared (0.35 vs. 0.86 mL/kg-min, respectively). The authors concluded that the extra back methylation path in neonates could largely account for the differences seen between neonates and adults. The results emphasize the importance of different metabolic pathways operating in neonates and infants during development.*

22. *Gentry et al. (2003) evaluated the impact of pharmacokinetic differences on tissue dosimetry during pregnancy and lactation with PBPK modeling. Six chemicals were investigated: isopropanol, vinyl chloride, DCM, perchloroethylene, nicotine, and TCDD.*

Model predicted differences in dosimetry during pregnancy were largely the result of the development of metabolic pathways in the fetus or changes in tissue composition in mother and fetus. Generally, predicted blood concentrations were lower in the neonate during lactation than in the fetus during gestation. Predicted fetal/neonatal exposures vs. maternal exposures ranged from 2-fold greater (TCDD) to several orders of magnitude lower (isopropanol). The results of this study are in general agreement with earlier studies namely that the "age range of greatest concern is clearly the perinatal period. The most important factor appears to be the potential for decreased clearance of toxic chemicals … due to immature metabolic enzyme systems".

Comment 4:

The potential for redundancy exists with applications of multiple uncertainty factors, resulting in UFs greater than or equal 3000-fold:

- For RELs based on systemic toxicity, the application of a UF is valid only when a reduction in the exposure level, as prescribed by the UF, results in a reduction in the internal dose at tissue of interest.

- The use of very large cumulative UFs (>3,000) in the low-dose region may not induce measurable changes in tissue concentrations. In which case, reduction in exposure concentrations is unnecessary, and the use of PBPK models should be discussed as an approach to assess target tissue dose and avoid excessive cumulative UFs.

- Consistent with USEPA approaches for setting RfCs, the total uncertainty factor should not exceed 3,000 because such uncertainty demonstrates that the available data are insufficient to set a standard.

The Technical Panel reviewing the USEPA RfD and RfC development process (EPA 2002) recommended that if there is uncertainty in more than four areas of extrapolation resulting in an cumulative UF of >3,000, it is unlikely that the database is sufficient to derive a reference value. Thus, it was recommended that the total UF applied to a chronic reference value for any chemical should not exceed 3,000. While OEHHA also notes 3,000 as an upper-bound for cumulative uncertainty factors, it is not identified as an absolute limit. Similar to the EPA approach, 3000 should be specified as a maximum without exceptions as there is overlap in the protection provided by multiple and large uncertainty factors.

Response:

As stated in the draft Technical Support Document, OEHHA agrees with the U.S. EPA conclusion that, if a cumulative uncertainty factor of greater than 3000 is indicated, the reliability of the resulting REL is likely to be low. This is not the same as arguing that a cumulative UF of 3000 is invariably sufficient to account for health concerns. OEHHA intends to regard this upper limit as general guidance, but does not consider it appropriate to make a blanket exclusionary statement which could never be overridden by any circumstances or data.

Comment 5:

Several UFs can be used to deal with data deficiencies, and these are assumed to overlap to some extent. On these bases, the USEPA Technical Panel agreed with the 10X Task Force Toxicology Working Group (U.S. EPA, 1999) that the 10-fold interspecies, intraspecies, and database deficiency UF values are adequate in most cases to cover concerns and uncertainties about children's health risks. OEHHA should further consider, on a chemical-bychemical basis, how the application of multiple uncertainty factors may result in unnecessarily low RELs and limit practical application in risk assessment.

Response:

OEHHA agrees that some types of data deficiency are covered by uncertainty factors such as those dealing with inter-or intra-species extrapolation, or extrapolation from a LOAEL to a NOAEL. The UF_D is proposed to deal with specific concerns, such as where a different endpoint from that observed in available studies is suspected. This may include concerns for children's health such as lack of developmental toxicity studies. OEHHA intends to use this uncertainty factor on a case-by-case basis, and only in response to specific criteria. We are revising the draft technical support document to clarify the circumstances in which this factor may be used.

Comment 6:

Implementation feasibility and scientific validity of RELs are of concern when the proposed RELs are equal or below background airborne concentrations. Comparisons of the proposed acute, 8-hr, and chronic RELs to the background air concentrations as reported by California Air Resource Board (CARB) were conducted. Exceedance of the RELs by background mean and 90^{th} percentile concentrations occurred for acrolein and manganese. For acetaldehyde, arsenic, formaldehyde, and mercury, background levels were comparable to the RELs. Oftentimes, maximum values (not illustrated in graphs below) measured for background air concentrations far exceeded the proposed RELs for all six chemicals. Background comparison is indicative as to whether the proposed REL is meaningful or overly protective.

Response:

The aim of REL development is to define a level which can reasonably be regarded as safe. . Thus, the REL can serve as an important indicator that ambient background exposures raise public healthconcerns or not. It is reassuring that there are only select cases where the background exposure to a toxicant of interest approach or exceed a REL; conversely, it is disturbing that there are a few cases where ambient exposures have been sufficiently well studied to be an indicator of a safe level. Existing background levels of some air pollutants are in fact shown to be unhealthy (e.g., ozone, particulate matter). The purpose of the REL under the Hot Spots program is to assist risk managers in determining what would be reasonable as an incremental emission by a facility. Any consideration of the existing background either locally or in general would be a matter for the risk manager to evaluate.

Recommendations of Additional Components and Comments to

the Proposed Revisions

We commend the advances made by the proposed revision to ensure adequate protection of children and infants, as well as other sensitive populations. We present the following recommendations that can provide critical information for appropriate scientific approaches in development of RELs:

Comment 7:

Recognition that RELs are only applicable to respirable particulates and gases should be explicitly made. Not all stationary source emissions are respirable. Risk assessment methodology is based on studies of the health effects of particles characterized as "respirable", which is conventionally defined as 10 μm or less; larger particles are not considered biologically relevant (Vincent 2005). As particle size and chemical speciation of emissions vary widely by type of facility and industry processes, particle characterization is critical to ascertaining the respirable fraction. For example, emissions from ferromanganese and dry-cell battery plants are predominantly particles of less than 2 μm mass median aerodynamic diameter (MMAD), whereas those from mining operations are characteristically larger (WHO, 1999). An estimated 20% of manganese in suspended particulate matter is characterized as particles greater than 5 μm (WHO 2004). Presumably, a lesser fraction than 20% is greater than 10 μm. Thus, this fraction of suspended particulate matter greater than 10 μm is not relevant to inhalation exposures and should not be considered for comparison with the REL. Although it is recognized that characterization of particle size is a component of exposure assessment, specifying that the RELs are protective of only respirable particulates clarifies the use of these toxicity criteria.

Response:

In evaluating RELs for volatile compounds it is assumed that inhalation exposure is via the dispersed gas phase. For particles, we had intended it to be implicit in our treatment of particle deposition, whether by the HEC methodology or more sophisticated models, that it is the respirable fraction which is of concern. We will add a clarification to this effect to the relevant section of the draft Technical Support Document. Some other values (such as the oral RELs used to deal with chemicals requiring multimedia assessments as described in the Part IV Technical Support Document) deal with routes other than inhalation where even very large particle sizes may be relevant.

Certain specific cases where the specification of particle size is important in defining toxicity are recognized, and these will be dealt with in the development of the specific RELs, as has already been done in the case of the chronic REL for respirable crystalline silica. It is worth noting that in this case the relevant definition is not PM_{10}, but the more restrictive definition of respirable particles by the NIOSH method. This emphasizes the importance of dealing with this question on a case-by-case basis.

More general considerations affecting exposure assessment are addressed by air dispersion modeling. These models are specified to describe the emissions from stacks of chemicals in the particle phase with aerodynamic diameters 10 μm or less, as described in the Part IV (Exposure Assessment and Stochastic Analysis) technical support document.

Comment 8:

Explicit discussion of inclusion criteria for studies considered in development of RELs would facilitate standardization of data collection and strengthen the evaluation process of the weight of evidence. Although typical of the approach used to derive noncancer toxicity criteria in general, only a select few serve as a basis for derivation of the RELs. The scientific basis for the weighting of key studies merits explicit explanation. For example, Roels et al. (1992) is the reference study for which the RELs for manganese were derived. Crump and Rousseau (1999) is a follow-up study of the cohort population examined in Roels et al. (1992). The rationale for omitting this updated study was not offered in the technical guidance. A framework for data review as set out in Chapter 4.3 of USEPA (2002) should be incorporated in the technical guidance.

Response:

OEHHA believes that the description of the study selection process given in Section 4.1, which is based closely on the corresponding sections of the previous Acute and Chronic (Parts I and III) technical support documents, is adequate. Our previous use of this level of guidance has generally been considered appropriate, and we do not consider it useful to be overly prescriptive. However it should be noted that various specific reference sources such as U.S. EPA's published guidance and Good Laboratory Practice specifications, the National Academy of Sciences and other standard sources are referenced in our existing summary.

With respect to manganese, the Roels study cited in the REL demonstrated that manganese is neurotoxic in adults. The follow-up study by Crump and Rousseau suggested that some, but not all, of the neurobehavioral deficits observed by Roels ameliorated with time. While these results are interpreted by some to indicate that the neurotoxic effects of manganese are transient in adults, it is critical to note that these results are for adults exposed as adults. There is much less certainty about the extent and transience of manganese's neurodevelopmental toxicity following inhalation exposure in the very young, a time when neurological damage is more likely to be permanent. There is also uncertainty about how well the measures of neurotoxicity used by Roels and in follow-up studies reflect the extent of the underlying neurological damage. The follow-up studies were not originally included as they provided no insight into these concerns nor did they negate the conclusion that manganese is neurotoxic. However, we note the specific concern in regard to the draft manganese RELs, and will add appropriate explanatory details to the toxicity summary.

Comment 9:

Because 8-hour RELs are primarily applied for the purposes of assessing hazards to offsite adult workers and exposures to children are not typically expected in industrial/commercial sites, OEHHA should consider limiting the application of 8-hour RELs to offsite workers in industrial/commercial areas. The additional UFs designed for the protection of children and infants may not be relevant in the majority of applications of 8-hour RELs. The current approved methodology for developing chronic RELs is more representative of exposure conditions for children and infants. While nonresidential areas could include schools or day care facilities, those facilities must be specifically identified and addressed in AB2588 risk assessment as

sensitive receptors. Thus, for these sensitive receptors, application of chronic RELs is appropriate and sufficiently protective of children and infants.

Response:

OEHHA agrees that there is a need for 8-hour RELs specifically applicable to offsite workers. Some of the circumstances for which 8-hour RELs may be applied may include statutory provisions excluding infants and children (such as workplaces), whereas others (such as school or day-care facilities) may explicitly include children in their exposed population. It must however be remembered that purely "occupational" adult-only scenarios still need to consider the possibility of exposure to a pregnant woman and her fetus, so the possibility of developmental toxicity in utero *still needs to be considered in this case.*

OEHHA therefore will develop two separate 8-hour RELs, one with the child-specific models or uncertainty factors, and another using adult appropriate factors and models (but including fetal sensitivity for developmental toxicants) for use with adults only. Depending on the details of the individual derivation this might be a matter of changing the values of uncertainty factors or a more complex adjustment. Guidance on the circumstances in which these versions of the 8-hour REL should be applied will be given in the forthcoming revision of the Part IV (Exposure Assessment and Stochastic Analysis) technical support document.

Comment 10:

The application of UFs for chemicals categorized as essential nutrients should be limited. The human body has metabolic components that can accommodate large fluctuations in the intake of essential nutrients. The criteria for evaluating essential elements must differ from those applied to conventional chemicals because uptake may be affected by nutritional status (IOM 2002). For example, zinc is an essential nutrient that is present in a wide variety of foodstuffs, and ubiquitous in the environment as major element in the earth's crust. Its intake is required for the proper growth, development, and maintenance of human health. To ensure adequate body stores of nutrients, the body is highly responsive to the intake levels of zinc, and adjusts absorption and elimination of zinc to maintain a relatively constant supply. In cases of unusually low intake, the body regulates zinc levels by increasing absorption and retention. Conversely, in cases of unusually high intake, the body regulates zinc levels by limiting absorption and increasing elimination. Such homeostatic controls enable the body to accommodate large fluctuations in the intake of essential nutrients, and remain markedly similar across mammalian species (Kim et al. 2004; King et al. 2000). On this basis, the general application of interspecies UF for toxicokinetic differences may be deemed unnecessary for chemicals categorized as essential nutrients.

Response:

OEHHA agrees that the consideration of RELs for essential nutrients is complicated. Although we agree with the specific points made about zinc as an example of an essential nutrient, we wish to point out that these particular features applicable to zinc cannot be generalized to other essential nutrients. Thus some elements with important roles (such as fluoride, which contributes importantly to development of caries-resistant tooth enamel) appear to have

extremely narrow margins of safety between a level which provides an optimum response and one where toxicity may be observed in at least some members of the population. Other well-known essential elements, such as iron and copper, show sufficient variation in environmental or dietary levels that both deficiency and excess symptoms are observed in different human populations. The picture becomes even more complex when, as is often the case, there are significant differences in bioavailability, distribution and even the nature of the toxicity between exposures to the same element by different routes. Intake of elements in support of an essential metabolic role is normally restricted to the oral (dietary and drinking water) route. In contrast, the route of intake of concern to the Air Toxics Hot Spots program is primarily inhalation, for which deposition and local toxicity in the lung are critical issues. In view of these complexities OEHHA considers it appropriate to deal with essential elements on a case-by-case basis, rather than attempting to include general guidance in the technical support documents.

Comment 11:

RELs should be compared to dietary intakes to determine whether the use of uncertainty factors or toxicity literature used to derive the point of departure results in unrealistically conservative values. For example, the arsenic REL is equivalent to an oral dose (oral REL) of 0.0035 μg/kg-day, which is nearly 70- times lower than the background dietary intake level of arsenic in American children (Tsuji et al. 2007). This suggests that the REL is overly conservative and well below background exposures. Tsuji et al. (2004) reviewed the scientific literature available for risk assessment of childhood exposures to arsenic. The study used by OEHHA as the point of departure (Wasserman et al. 2004) was not included in Tsuji et al. (2004) because both papers were published in 2004. However, in the review of similar literature, the critical parameters (i.e., neurological outcome data from children in developing countries) that were considered by Tsuji et al. (2004) are comparable to the Wasserman et al (2004) study. Results of Tsuji et al. (2004) indicate a different point of departure. Tsuji et al. (2004) concludes that the LOAEL for adverse health effects from both acute and subchronic exposure in children is 50 μg/kg-day and that the reference exposure level for subchronic exposure in young children is 5 μg/kg-day, which is more than 1,000 higher than the subchronic oral REL developed by OEHHA.

Response:

It is important to bear in mind that for many toxic chemicals of concern to the Air Toxics Hot Spots program there are major differences in toxicity depending on the route of exposure, in which case comparison of dietary intakes to REL values is possibly interesting, but irrelevant to evaluating the "conservatism" of the REL. This applies not only to cases where different toxicities are observed at the site of first contact for different routes, but also for systemic toxicants where large differences in bioavailability may apply. In addition for toxic elements, the chemical form (soluble salts vs. insoluble salts, oxides, organics etc.) may be distinctly different for inhaled environmental pollutants as compared to dietary sources.

As noted in the comment, Tsuji et al. *(2004) have proposed child acute (< 1 yr) and subchronic (1-12 yr) reference levels of 0.015 mg/kg-d and 0.005 mg/kg-d, respectively. These values (as much as 250 μg As/day in a 50 kg 12 year old) are higher than the values derived in the present study (15 μg/d for visual perception and 7 μg/d for skin effects). The major differences between Tsuji* et al. *(2004) and the present study are methodology and study selection. Tsuji et al.*

applied uncertainty factors of 3 or 10 to LOAELs from studies on skin effects to derive NOAELs and proposed reference levels. The additional UF of 3 was assumed to account for other arsenic-induced effects including neurological effects. These authors did not attempt to quantitate adverse effects through dose response analysis. Our study employs a benchmark dose quantitative approach and focuses on neurotoxicity as the adverse effect of concern for chronic exposures. In our methodology, exposures to children of 8 years duration or greater are considered chronic exposures (12 % of 70 yr), not subchronic. We employed uncertainty factors of 10 to 30 for inter-individual variation since we could not assume that the small study populations accurately reflected the variation seen in much larger populations to which reference levels may apply. It should also be noted that the epidemiological evidence for human toxic effects derives from either drinking water and/or inhalation exposure studies. Internal arsenic dosimetry via these sources/routes may differ from that related to dietary intake due to different kinetics, exposure patterns and chemical forms of arsenic.

Comment 12:

Conclusions

We commend the advances and proposed revisions offered by this draft guidance. In keeping with legislative mandates, the proposed revisions represent OEHHA's continuing efforts to refine risk assessment methodology and to protect children and infants health. We concur with OEHHA that scientific evidence indicates that metabolic differences between children and adults exist, and thus, may result in differential susceptibility—both greater and lesser susceptibility. While recognizing that health-protective regulatory exposure limits are designed to be conservative so that they are adequately protective of susceptible populations, incorporation of uncertainty factors (UFs), in the absence of adequate data and insufficiently developed justifications for application of consecutive UFs, warrant strong caution. Consistent with OEHHA's mandate, all relevant scientific data must be considered for scientific approaches in developing the RELs. OEHHA's preference for PBPK modeling over use of UFs is progressive, and should be used to the greatest extent feasible to improve the basis of the RELs. Explicit recognition that RELs are only applicable to the respirable particulates and gases, the delineation of specific inclusion criteria for studies considered, and other efforts to incorporate recent technological and research developments are recommended. Collectively, the proposed revisions to the methods and new risk assessment components have the potential to be powerful tools to better incorporate the significance of various life stages and susceptible subpopulations into the risk assessment process. We hope that the attached comments contribute to the progressive and science-driven process developed by OEHHA, and help to ensure that the Agency undertakes the most appropriate and scientifically valid approach in developing the RELs.

Response:

OEHHA thanks Exponent for the time spent reviewing the document and for sending in their comments.

Comments of Betsy M. Natz, on behalf of the Formaldehyde Council, Inc.

The Formaldehyde Council, Inc. (FCI) appreciates the opportunity to submit comments on the Office of Environmental Health Hazard Assessment (OEHHA) draft document, Air Toxics Hot Spots Program Technical Support Document (TSD) for the Derivation of Noncancer Reference Exposure Levels and, specifically, the acute and chronic Reference Exposure Levels (RELs) for formaldehyde and the updated the health protective levels for these compounds.

FCI has a unique and expert understanding of the science of formaldehyde toxicology and applicable risk assessment models.[1] FCI members have invested considerable resources in advancing the understanding of formaldehyde toxicology, which gives FCI a comprehensive view of the science surrounding formaldehyde.

OEHHA's proposed formaldehyde Acute REL of 55 μg/m³ (44 ppb) for mild and moderate eye irritation is based on Kulle et al. (1987), as is the 8-Hour REL of 9 μg/m³ (7 ppb), and the Chronic REL of 9 μg/m³ (7 ppb) is based on Wilhelmsson and Holmstrom (1992) for asthma-like respiratory symptoms. The derivation of each of the three RELs includes the application of an intraspecies uncertainty factor of 10 for Toxicodynamic (UFH-d) based on asthma exacerbation in children.

FCI's primary observation, based on an evaluation of the literature relating to formaldehyde exposure and asthma or asthma-like effects, the uncertainty factor of 10 for UFH-d should be changed to 1 for all three RELs. This change is further supported by other expert reviews and the endogenous nature of formaldehyde in relation to human metabolism, which appear to have been overlooked in preparation of the draft RELs. Collectively, this information suggests that the Cumulative Uncertainty Factors of 10 and 60 should also be revisited and reduced.

Comment 1:

I. Asthma Induction and Allergic Sensitization

OEHHA's proposed conclusions with respect to asthma and formaldehyde are not representative of the weight of evidence, which is discussed in Arts et al. (2006), Paustenbach et al. (1997) and Bender (2002), as described below.[2] In addition, the proposed conclusion with regard to formaldehyde and asthma is at odds with the Agency for Toxic Substances and Disease Registry

[1] FCI is a trade association of leading producers and users of formaldehyde that is dedicated to promoting the responsible use and benefits of formaldehyde and ensuring its accurate scientific evaluation. For more information please see *http://www.formaldehyde.org*.

[2] FCI recognizes that OEHHA avoids the use of reviews as a basis for setting RELs. Our reference to reviews is not intended to challenge OEHHA's methodology in this regard. Rather, if a number of different expert reviews reach different conclusions from the draft document, this provides compelling evidence that OEHHA has erred in its interpretation of the rich and often complex body of scientific studies relating to formaldehyde.

(ATSDR), the National Academy of Sciences and the Organization for Economic Cooperation and Development (OECD).

- OECD (2002), consisting of regulators from thirty countries, reviewed formaldehyde under its Existing Chemicals program and concluded that "[m]ost studies show no effect on lung function in either asthmatics or non-asthmatics."[3]
- A report by the National Academy of Sciences' Institute of Medicine (IOM 2000) similarly found inadequate evidence of any association between formaldehyde exposure and asthma induction. Several clinical investigations of asthma cases suspected to be due to formaldehyde failed to confirm even a single case based on inhalation challenge tests.[4]

ATSDR (1999) states that investigations into formaldehyde and asthma provide very limited evidence of an association.

Although the draft TSD repeatedly asserts an association between low level exposure to formaldehyde and that the development of allergic sensitization is biologically plausible, formaldehyde exposure has not been shown to cause or exacerbate asthma. By way of example, Dr. Frigas and others at the Mayo Clinic conducted bronchial challenge tests with formaldehyde in 13 patients suspected of having formaldehyde-induced asthma. In Frigas et al. (1984), the authors concluded: "[T]esting with a formaldehyde bronchial challenge did not provoke asthma in 13 selected patients with symptoms suggestive of asthma and a history of exposure to formaldehyde gas. Cases of formaldehyde-induced asthma may be rare." Grammer et al. (1993) concluded that immunologically-mediated asthma caused by formaldehyde is extremely rare, if it exists at all. Witek et al. concluded that in mild asthmatics, short term (40 minute) exposure to 2 ppm does not induce acute airway obstruction. In a study by Pross et al. (1987) no effect on the immune response was observed in asthmatic subjects exposed to formaldehyde at 1 ppm.

The NAS study of submariners and their long-term, continuous exposure to formaldehyde (discussed above) states that a controlled study in asthmatic subjects (Harving et al. 1990) found no association between subjective ratings of sensory irritation and increasing formaldehyde exposures at concentrations from 0, 0.01, 0.1, and 0.69 ppm.[5] The study also explains that at levels lower than 3 ppm, "asthmatic individuals exposed to airborne formaldehyde do not appear to be at greater risk of suffering airway dysfunction than nonasthmatic individuals."[6] Paustenbach *et al*. (1997) cite a number of studies leading them to conclude asthmatics are no more sensitive to formaldehyde than healthy individuals, including studies by Sheppard (1986), Sauder (1987), Green (1987) and Kulle (1987 and 1993). Paustenbach's reading of Kulle markedly differs from that of the proposed guidelines document.

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[3] OECD (2002) (at 16) notes: "Formaldehyde induced asthma as been studied and findings from detailed clinical evaluations of suspected subjects suggest that it is rare, if it exists at all."

[4] *See, e.g.*, Frigas et al. (1984); Grammer et al. (1993); and Krakowiak et al. (1998).

[5] *Id*. at 86.

[6] *Id*. at 87.

As seen by the above, the weight of the scientific evidence supports a lack of association between formaldehyde exposure and asthma induction or exacerbation. Accordingly, the statements regarding formaldehyde and asthma should be revised in the final TSD.

Response 1:

The formaldehyde Reference Exposure Level (REL) summary cites the Frigas et al. (1984) study as well as most of the others mentioned in the comment. Indeed, OEHHA reflects the findings of those studies saying, "The major findings in these studies were mild to moderate eye and upper respiratory tract irritation typical of mild discomfort from formaldehyde exposure." Further, the newer studies evaluating associations between formaldehyde exposure in the home and respiratory symptoms in children were published mostly after the IOM (2000) and ATSDR (1999) reviews. ATSDR does not conclude there is no evidence of an association between asthma and formaldehyde exposure.

In addition, there are animal studies indicating that formaldehyde inhalation alters the immune response to allergens, often resulting in hypersensitivity. In mice, continuous exposure to formaldehyde inhalation significantly enhanced and prolonged a contact hypersensitivity response (Fugii et al., 2005), while in mice exposed to 2000 ppb formaldehyde, the numbers of total bronchoalveolar lavage cells, macrophages, and eosinophils were significantly increased compared to 0 ppb controls (Fujimaki et al., 2004). Thus, while questions remain regarding the extent to which formaldehyde by itself induces asthma, it appears to have a possibly substantial role in the potentiation of the allergic response to household allergens.

Comment 2:
Potential for differential effects

Based on the discussion in the draft TSD, OEHHA appears to suggest that children are more affected than adults by formaldehyde exposure. If so, there are many questions concerning the validity of the studies cited by OEHHA, and we would ask that the agency reconsider the use of these studies. Three of the studies cited (Franklin *et al.* (2000), Garret *et al.* (1999) and Wantke *et al.* (1996)) do not contain data on adults and cannot serve as a basis for establishing the relative sensitivity of children and adults. In addition and as explained below, contradictory finding across studies raise questions concerning the general applicability or validity of the findings to the general population.

IOM (2000)

The proposed TSD does not appear to consider a major report prepared by the National Academy of Sciences Institute of Medicine (IOM) that bears directly on the issues raised by the other studies in the proposed guidelines document and does not support OEHHA's proposed conclusions regarding asthma. This report, entitled "Clearing the Air: Asthma and Indoor Air Exposures," was prepared by 12 experts in the field and a committee was chaired by Professor Johnston, M.D., Department of Pediatrics, University of Colorado School of Medicine. It examined the evidence regarding the association between indoor biologic and chemical exposures and development of asthma. The Committee discussed asthma among the general population and in sensitive subpopulations including children, and concluded that only one

agent, house dust mite allergen, had "Sufficient Evidence of a Causal Relationship." In the next category, the only agent found to have a "Sufficient Evidence of an Association" was Environmental Tobacco Smoke in preschool-aged children.

The Committee also reviewed evidence regarding the association between indoor biologic and chemical exposures and the exacerbation of asthma in sensitive individuals. In this case, the agents in the category "Sufficient Evidence of a Causal Relationship" were found to be environmental tobacco smoke in preschool-aged children, house dust mite allergen, cockroach allergen, and cat allergens. Agents in the next category of "Sufficient Evidence of an Association" were found to be nitrogen dioxide; NO_x (high-level exposures at concentrations that may occur only when gas appliances are used in poorly ventilated kitchens); rhinovirus; dog allergens; and fungi/mold allergens. The Committee also found that a variety of strategies, such as removing a pet, intensive cleaning, prohibiting smoking and controlling indoor humidity might help alleviate asthma symptoms.

Further, according to the IOM report, several of the other studies in this area, which are cited by OEHHA fail to identify causative agents with substantial evidence in children and/or have not controlled for variables, such as humidity/dampness, identified as important confounding factors in the IOM report.

Response 2:

First, we do not conclude that there is a causal association between formaldehyde exposure and asthma induction. We indicate that there is evidence of an association between exposure to formaldehyde and asthma-like symptoms in children. While there are limitations to the studies we cite, they point to a significant uncertainty. It should be noted that most of these studies were not available at the time of the IOM review.

With respect to the IOM review, the IOM 2000 report put formaldehyde into the category of "Inadequate or insufficient evidence to determine whether or not an association exists between formaldehyde exposure and asthma development." In the context of asthma exacerbation, IOM elevated formaldehyde to "Limited or suggestive evidence of an association between formaldehyde exposure and wheezing and other respiratory symptoms." Thus, for the IOM Committee, there remains uncertainty regarding the role of formaldehyde in asthma but they recognize that evidence suggests an association with asthma exacerbation.

We have included exacerbation of asthma as a toxicological endpoint of particular concern to children. Asthma surveillance data developed by the national Centers for Disease Control and Prevention (CDC) (Mannino et al., 1998) and reports on asthma hospitalization by the California Department of Health Services (CDHS, 2000) both indicate that children, especially young children, are impacted by asthma morbidity more than older children and adults. The prevalence rates statistics indicate that a significantly higher percentage of children have asthma than adults (Mannino et al., 1998). The Centers for Disease Control report asthma prevalence rates per 1000 persons from their National Health Interview Survey by age group of 57.8 for 0-4 year olds, 74.4 for 5-14 year olds, 51.8 for 15-34 year olds, 44.4 for 35-64 year olds and 44.6 for over 65 years. In addition, children have smaller airways than adults. Since the resistance to airflow is inversely proportional to the fourth power of the radius,

bronchoconstriction and increased mucin secretion characteristic of asthma greatly increase airflow resistance in a small child relative to an adult. Thus, breathing difficulty is very significant in young children experiencing an asthma attack. The hospitalization rate for children 0 to 4 years is greater than all other age groupings (see Table 3), and is four- fold higher for black children than for white children (CDHS, 2000). Hospitalization, a nondiscretionary event, occurs only in severe cases. While hospitalization rate data are influenced by a number of factors including access to health care, we believe this information supports the concern that asthma impacts children more than adults.

Comment 3:

Franklin et al. (2000)

The Franklin et al. study (2000) measured exhaled nitric oxide as an indicator of subclinical inflammatory response in 224 Australian children. The authors report increased nitric oxide in the breath of children in homes with over 50 ppb versus under 50 ppb formaldehyde. The range and mean exposure values are not provided. There were no measurements of the outdoors or school exposures to these children. The nitric oxide results were independent of atopy, and thus their significance is unclear. The study showed formaldehyde concentrations in the home had no effect on FVC or FEV1 measures of pulmonary function in the children. The study does not compare children and adults, since relevant data for adults were not collected.

Response 3:

Franklin et al. (2000) states that eNO was used as an indicator of inflammation of the lower airways, and reported significantly higher exhaled NO in the breath of children living in homes with formaldehyde concentrations greater than 50 ppb than in the breath of those children living in homes with formaldehyde levels below 50 ppb. Since inflammation of the airways is a hallmark of asthma, this result indicates that formaldehyde might exacerbate an already chronically inflamed airway. Exhaled nitric oxide (NO) is not presented as a measure of atopy. The formaldehyde REL document does not assert that a comparison between adults and children was performed in this study. Rather, the document looks at whether there is evidence that formaldehyde exacerbates asthma-like symptoms in children, and evaluates the information from the overall literature regarding effect levels in adults and children.

Comment 4:

Krzyzanowski et al. (1990)

The proposed guidelines document cites a finding by Krzyzanowski et al. (1990) of a greater prevalence of asthma and chronic bronchitis in children whose houses had 60-120 ppb of formaldehyde. Researchers questioned a group of 298 children (ages 6 to 15) and 613 adults using a self-administered respiratory questionnaire. Using regression analysis, the investigators found no significant association between exposures in children and self-reported chronic respiratory symptoms.

Prevalence rates of chronic bronchitis or asthma reportedly diagnosed by a physician were significantly higher when residential concentrations of formaldehyde exceeded 60 ppb, especially in the presence of tobacco smoke. However, the study itself fails to point out an

obvious difficulty from the data displayed in Tables 3 and 4 of the study. There was no dose-response relationship with formaldehyde:

Prevalence Per 100 Subjects

Reported by Krzyzanowski in Tables 3 and 4

	≤ 40 ppb	**40-60**	**>60**
Chronic Bronchitis			
No Environmental Tobacco Smoke (ETS)	4.3 (n=141)	0 (n=12)	10.0 (n=10)
ETS	1.9 (n=106)	0 (n=10)	45.5 (n=11)
Asthma			
No ETS	8.5 (n=142)	8.3 (n=12)	0 (n=10)
ETS	15.1 (n=106)	0 (n=12)	45.5 (n=11)

More than 83 percent of the subjects in the study lived in homes in which the two-week average formaldehyde concentrations were less than 4 ppb. The average concentration measured was 26 ppb, with only a few homes exceeding 9 ppb. Thus, average concentrations appear to be driven by a few outliers. Findings of this study are questionable in view of these levels of formaldehyde found in the home environment. In addition, there were no measurements of allergens, or other agents present in the home.

The authors did report greater changes in peak expiratory flow rate in children than in adults. The use of peak expiratory flow rates does not confirm the presence or absence of asthma or bronchitis. This finding is the only data in any of the studies cited in the draft document to suggest differential effects in children versus adults -- hardly a convincing basis for concluding that children are more sensitive to formaldehyde. In sum, it appears that this study is at odds with the weight of the literature, and should not be relied upon absent some further verification.

Response 4:

In the study by Krzyzanowski et al. (1990), it is stated: "The authors note no threshold was found for formaldehyde effects on ventilatory function in the children, and that a 10% decrease in PEF was associated with exposures as low as 30 ppb in non-asthmatic children with an even larger effect in asthmatic children at 30 ppb". The comment notes that effects on peak expiratory flow rate are greater in children than in adults, but this "does not confirm the presence or absence of asthma or bronchitis." Reduced PEF is also characteristic of inflamed airways and asthma. This represents additional information that formaldehyde exposure may exacerbate breathing difficulties in children, especially those with asthma.

Regarding the absence of a dose-response in this study, we state in the formaldehyde REL document that no statistically significant association was found in this study. We also noted that the sample size in the 40-60 ppb group was small compared to the controls. There was a response in the no ETS group for the greater than 60 ppb group (10%). We accurately summarized the findings of this study including mentioning that the association was not statistically significant. However there was a significant p-trend reported.

While Krzyzanowski et al. (1990) is the only study that directly compares the effects of formaldehyde in adults and children, there are several other studies that indicate that children are more sensitive to formaldehyde toxicity than adults. Of the numerous studies in adults (primarily occupational studies) the NOAEL and LOAEL are 32 μg/m^3 (26 ppb) and 92 μg/m^3 (75 ppb), respectively, after adjustment for exposure continuity. (These data are based on nasal and eye irritation observed in Wilhelmsson and Holstrom (1992), and histological lesions in the nasal cavity documented in Edling et al. (1988). The data form the basis of the chronic REL, described in detail in OEHHA (2000)). However, studies in children, including the Krzyzanowski study above, indicate adverse health impacts in children at concentrations as low as 30 ppb.

Comment 5:

Wantke et al. (1996)

Wantke et al. (1996) studied 62 students in Austria and reported finding IgE specific to formaldehyde.[7] However, among the 24 of the 62 children who had elevated IgE specific to formaldehyde, only 3 had RAST scores over 2.0.[8] There was no dose-response relationship between formaldehyde levels and RAST scores. The three classrooms studied had 43, 69 and 75 ppb of formaldehyde measured, respectively. RAST scores were not elevated at 69 ppb compared to the 43 ppb classroom, as shown below.

Number of Students with Specific IgE to Formaldehyde in Wantke, Table 2

	75 ppb (n=22)	69 ppb (n=22)	43 ppb (n=18)
RAST over 2.0	2	0	1
RAST 1.3-1.9	10	6	5
RAST 1.0-1.2	10	16	12

Thus, there does not appear to be dose-response relationship between formaldehyde and IgE. Moreover, the IgE levels in the study did not correlate with either number or severity of reported

[7] IgE refers to Immunoglobulin E, a class of immunoglobulins that includes the antibodies elicited by an allergic substance (allergen). A person who has an allergy usually has elevated blood levels of IgE. The E in IgE stands for erythema (redness).

[8] RAST stands for RadioAllergoSorbent Test. A sample of blood is mixed with substances known to trigger allergies. The test measures the level of allergy antibodies (specific IgE antibodies) in the blood which are present if there is a allergic reaction.

symptoms. The authors acknowledge that "IgE-mediated sensitization to formaldehyde is rare and a matter of controversy." They further state: "Our data as well as the literature [ref. omitted] do not conclusively explain the clinical relevance of specific IgE against formaldehyde." The Wantke *et al.* study did not compare children and adults, and thus also does not speak to any differential sensitivity.

Response 5:

The formaldehyde REL document does not rely on the results of the Wantke et al. (1996) study. The conclusion of the Wantke et al. (1996) study stated, "Gaseous formaldehyde, besides its irritant action, leads to IgE-mediated sensitization. By itself, the odds ratio referenced in the above study is taken as suggestive of an association. The formaldehyde REL document does not assert statistical significance associated with this result. However this study does suggest an association and states: "There was a good correlation between symptoms and the formaldehyde concentrations in the classrooms." Wantke et al. (1996) reported that formaldehyde-specific IgE and respiratory symptoms were significantly reduced when children transferred from schools with formaldehyde concentrations of 43 to 75 ppb to schools with concentrations of 23 to 29 ppb (p values ranged from <0.05 to <0.001). These studies are used as supportive studies, not as the basis for causal evidence. As for formaldehyde and IgG, the formaldehyde REL document review of the Wantke et al. (1996) notes the lack of apparent dose response. However, the more telling comparison is the significant (p<0.002) decrease in IgG following the children's move to lower formaldehyde levels in the new school.

Comment 6:

Garrett et al. (1999)

Garrett et al. (1999) is a study of asthmatic and non-asthmatic children in two small towns in Victoria, Australia. This paper does not address differences in adult and children's responses, since relevant data for adults were not collected. It does characterize the Wantke *et al.* (1996) study relevance as "unclear" because the sensitization was not associated with symptoms. Several factors compel caution in relying on this study:

- The paper likely was based on a graduate student thesis (the acknowledgements note a postgraduate publication award), and the paper presents extensive multi-variate analysis. Of all the analyses performed, the study notes:

    1. a crude odds ratio for atopy of about 1.4 with an increase in bedroom levels of formaldehyde of 10 ug/m3 (adjusted for parental asthma and sex); however, the confidence interval for this finding is 0.99 - 2.00; and

    2. an adjusted odds ratio of 1.42 for atopy with an increase in the highest recorded formaldehyde level by 20 ug/m3 (confidence interval 0.99-2.04). (As the majority of scientists and researchers recognize, odds ratios of 1.4 are generally not considered to be strong evidence of a causal connection.)

- The study took place in two small towns "surrounded by open-cut brown coal mines and power stations, which provide considerable employment." The authors had difficulty

locating nonasthmatic children to participate in the study. Outdoor measurements were taken but not reported.

- The authors note there was no significant association between formaldehyde levels and house age. This is surprising, since any off gassing of formaldehyde from wood products or other formaldehyde-containing materials would be expected to decline over time. Thus, the accuracy of formaldehyde measurements could be open to question.

- In discussing the implications of their findings, Garrett et al. note the increased prevalence of allergic diseases in many Western countries, and suggest that materials emitting formaldehyde have become increasingly popular at the same time. The authors apparently do not appreciate that formaldehyde resin technologies have been improved substantially over the last two decades, and that releases of formaldehyde have been greatly reduced.

- It is difficult to rule out systematic recall or selection bias in this case-control study.

- With respect to exposure issues, no personal monitors were used, and there were no associations or trends for levels reported for the bedrooms, which are the one place in the house where some form of continuous exposure is likely to occur.

- The distribution of results claimed by the investigators hardly seems to be persuasive evidence of a systematic health risk. There was no significant increase in the adjusted risk for either asthma or respiratory symptoms with increasing formaldehyde exposure.

Response 6:

Garrett et al. (1999) reported increased sensitization associated with the formaldehyde level in children's homes which had a median value of 15.8 μg/m^3 (12.6 ppb). In the formaldehyde REL summary, OEHHA does not base its chronic REL on the Garrett et al (1999) study. The study did report that outdoor measurements were lower than indoor. With respect to the off-gassing of formaldehyde over time and whether the formaldehyde measurements are questionable as a result, no supporting evidence is provided for this speculation. Regarding the assertion that formaldehyde resin technologies have improved over time, OEHHA does not see the relevancy of this statement to the formaldehyde REL document. The concern about selection and recall bias is not particularly germane as the study was investigating the association between measured levels of formaldehyde and objective measures of allergic response (atopy, positive skin prick tests and maximum wheal size). Regarding the assertion that there was no significant increase in adjusted risk for asthma or respiratory symptoms, there is a p-trend for this that, although not statistically significant, indicated a biologically important association.

With respect to the size of the odds ratio a statistically significant strong association, such as measured by a high relative risk, between a factor and a disease is often viewed as an important criterion for inferring causality because, all other things being equal, a strong association makes alternative explanations for the disease less likely. However, as discussed in Rothman and Greenland (1998), the fact that a relative risk is small in magnitude does not rule out causality. The important factors to consider include the strength of the study design (particularly

controlling for confounding variables, obtaining an unbiased sample, measurement error) and the level of statistical significance. There are a number of examples of statistically significant small magnitude associations that are widely accepted as causal such as the causal links between air pollution and cardiovascular/pulmonary mortality, and passive smoking and lung cancer. From a public health perspective, even a small magnitude increase in risk for a common disease can mean large numbers of people affected by the health outcome when exposure is frequent and widespread.

Comment 7:

Rumchev et al. (2002) and (2004)

In Rumchev, et al. (2002), household formaldehyde levels were determined by passive sampling in the homes of 88 children aged 6 months to 3 years who were diagnosed at a hospital with asthma, and compared with 104 community controls. Cases had a statistically significant higher mean formaldehyde exposure compared to controls, 32 ppb (38 $\mu g/m^3$) and 20 ppb (24 $\mu g/m^3$), respectively. After adjustment for confounding factors, such as indoor air pollutants, relative humidity, indoor temperature, atopy, family history of asthma, age, sex socioeconomic status, pets and environmental tobacco smoke, Rumchev et al. (2002) reported that children exposed to formaldehyde levels of 60 $\mu g/m^3$ had a 39% increase in odds of having asthma compared to children exposed to less than 10 $\mu g/m^3$ (or estimated to be approximately 1.4 95% CI 1.1-1.7 from data presented in a graph). However, considering the marginally increased risk observed, together with the number of potential sources of bias, such as selection bias and validity of diagnosis in the young, this study should not be considered sufficiently robust evidence of an association between formaldehyde exposure and increased risk of asthma in children or an appropriate basis for regulation or governmental guidance.

In addition, as noted previously, formaldehyde is exhaled in the breath, with studies suggesting that breath levels may range from 1.2 - 72.7 ppb to 300 – 1,200 ppb (Moser et al. 2005; Ebeler et al. 1997). Based on the existing literature, the exposure levels reported in Rumchev et al. (2002) are in the range of formaldehyde expected to be found in exhaled breath. This raises the questions of causation, association, and how one might reasonably differentiate self-exposure from an exogenous source of exposure at approximately the same concentration.

Those limitations and weaknesses are validated by a second report by Rumchev, et al. (2004), which raises questions regarding whether Rumchev (2002) is an adequate basis for the derivation of a reference concentration specifically for formaldehyde. Rumchev, et al. (2004) used the same cohort of children and evaluated the same asthma endpoint as Rumchev, et al. (2002), but focused on the association with the other chemicals and particulates rather than formaldehyde. As for formaldehyde, Rumchev, et al. (2004), found that asthmatic cases were exposed to higher levels of volatile organic compounds (VOCs).

An editorial was published concurrently (Brunekreef, B. 2004) with Rumchev et al. (2004), which focused on nitrogen dioxide (NO_2), VOCs, and particulates. The editorial indicates that (1) diagnosis of asthma in children is "notoriously difficult," and (2) case-control studies, as used by Rumchev, inherently are rife with potential and actual sources of confounding and bias. An example given is that Rumchev et al. (2004) did not attempt to evaluate the impact of recent

indoor painting. These issues raise serious questions regarding the adequacy of the study as a sole source for deriving a reference exposure.

Response 7:

The Rumchev study supports an association with exposure to formaldehyde and the observation of asthma-like symptoms in children. However, it was not selected for REL development due to the difficulties in distinguishing asthma from other wheezing conditions in the clinical diagnoses in such a young population. There are additional uncertainties associated with the exposure continuity, and we recognize the limitations of the study, such as the possibility of observational and/or recall bias in the parental reports of respiratory symptoms characteristic of asthma.

The formaldehyde REL summary lists the confounders mentioned in the Rumchev study ("Estimates of the relative risk for asthma (odds ratios) were adjusted for measured indoor air pollutants, relative humidity, temperature, atopy (hereditary allergy), family history of asthma, age, gender, socioeconomic status, pets, smoke exposure, air conditioning, and gas appliances") (Rumchev et al., 2002). This study found statistically significant increase in asthma symptoms associated with formaldehyde. Thus, within the limitations noted by the authors, this study provides evidence for an association between formaldehyde exposure in children and asthma.

OEHHA is aware of the Rumchev et al (2004) paper because of our general interest in childhood asthma, but did not cite it in the staff report because it concerns only volatile organic compounds (VOCs) other than formaldehyde. The comment misquotes the paper in implying that the finding of links between asthma and VOCs undermine the earlier finding of an association with formaldehyde. The authors note in discussion that they specifically examined this question by comparing their VOC data with the previously published formaldehyde data. They concluded that the two effects were independent.

With respect to exhaled formaldehyde, based on recent methodology, formaldehyde levels in breath are generally in the low ppb range in healthy people, while higher levels appear to be associated with disease states such as inflammation or cancer which enhance lipid peroxidation. The values from Moser (1.2 - 72.7 ppb; median 4.26 ppb) for human breath are compared with values ARB has for conventional homes of 13.9 ppb on average, with the maximum >200 ppb. (Moser et al., 2005).

Comment 8:

Conclusion on Asthma

As Brunekreef (2004) noted in his comments on Rumchev et al. (2004) and other studies:

> The issue of whether indoor VOCs are a risk factor for asthma in children therefore seems still to be largely undecided. In view of the methodological difficulties outlined above, prospective studies are more likely to produce progress in deciding whether we need to worry about indoor VOCs as determinants of asthma at the relatively low concentrations typically encountered in the home environment.

In view of the issues raised by Rumchev (2004) showing that a number of VOCs were associated with asthma as well as the inherent and broader limitations associated with Rumchev et al. (2002), Rumchev, et al. (2002) does not provide a reasonable basis for adopting a new level. A careful reading of the studies cited as the basis for concluding that children are differentially sensitive to formaldehyde shows essentially no support for that proposition. [9]

Response 8:

OEHHA considers that asthma adversely impacts children more than adults and thus substances that may either exacerbate or induce asthma should be considered for listing under SB 25. While chamber studies in adults have not been convincing that formaldehyde exposure exacerbates asthma, the studies in adults may not be applicable to allergic asthma in children. As previously noted, Krzyzanowski et al. (1990) found that asthmatic children were more affected by formaldehyde than non-asthmatic children. In addition, allergic sensitization, as measured by elevated levels of formaldehyde-specific IgE, has been noted in two studies of children exposed to environmental levels of formaldehyde (Wantke et al., 1996; Garrett et al., 1999). The allergic sensitization may make children more sensitive to development of serious conditions such as asthma, although this has not been studied for formaldehyde. As noted in the response to the previous comment, Rumchev et al. (2002) found a statistically significant association between asthma symptoms and formaldehyde exposure in children. In addition to the data in children, animal data provide support for the contention that formaldehyde exposure may exacerbate asthma. Amdur (1960) showed that formaldehyde has a marked effect on airway resistance and compliance in guinea pigs. More importantly, Sweicechowski et al. (1993) showed that duration of exposure is important to the induction of airway hyperreactivity from formaldehyde. In this latter study, an 8-hour exposure to 1 ppm formaldehyde produced greater than expected effects on airway constriction compared to a 2-hour exposure at higher concentrations, suggesting that prolonged, low-level formaldehyde exposures may generate abnormal physiologic responses in the airways not detectable after acute exposures.

In addition to the human and animal studies of formaldehyde toxicity, OEHHA also considered exposure. Typical urban ambient air levels and indoor air levels can exceed the chronic REL of 2 ppb. Moreover, children are frequently exposed to levels of formaldehyde exceeding the chronic REL in indoor air of classrooms. A compilation of monitored California classrooms showed that children were exposed to a mean of 21 ppb and a maximum of 98 ppb (CARB, 2001, interdepartmental transmission). For these reasons, formaldehyde is considered a priority chemical for evaluation of potential differential effects on infants and children.

As mentioned in the responses to comment #2, we have included exacerbation of asthma as a toxicological endpoint of particular concern to children. Asthma surveillance data developed by the national Centers for Disease Control and Prevention (CDC) (Mannino et al., 1998) and reports on asthma hospitalization by the California Department of Health Services (CDHS,

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[9]Sufficient evidence of a causal relationship or an association with asthma only exists for cats, cockroaches, house dust mites, ETS (preschoolers), dogs, fungi or molds (Rhinovirus) and high-level exposures to nitrogen oxides, not formaldehyde or other VOCs. For an elaboration, see the National Research Council (2004) *Emergency and Continuous Exposure Guidance Levels for Selected Submarine Contaminants,* p. 87.

2000) both indicate that children, especially young children, are impacted by asthma morbidity more than older children and adults. The prevalence rates statistics indicate that a significantly higher percentage of children have asthma than adults (Mannino et al., 1998). The Centers for Disease Control report asthma prevalence rates per 1000 persons from their National Health Interview Survey by age group of 57.8 for 0-4 year olds, 74.4 for 5-14 year olds, 51.8 for 15-34 year olds, 44.4 for 35-64 year olds and 44.6 for over 65 years. In addition, children have smaller airways than adults. Since the resistance to airflow is inversely proportional to the fourth power of the radius, bronchoconstriction and increased mucin secretion characteristic of asthma greatly increase airflow resistance in a small child relative to an adult. Thus, breathing difficulty is very significant in young children experiencing an asthma attack. The hospitalization rate for children 0 to 4 years is greater than all other age groupings (see Table 3), and is four-fold higher for black children than for white children (CDHS, 2000). Hospitalization, a nondiscretionary event, occurs only in severe cases. While hospitalization rate data are influenced by a number of factors including access to health care, we believe this information supports the concern that asthma impacts children more than adults.

Evaluating Acute Health Effects

Comment 9:
Sensory Irritation and Formaldehyde

There is a robust database on the dose-response characteristics of formaldehyde induced sensory irritation. Reviews of the formaldehyde literature have noted that the most sensitive endpoints reported are for eye and upper respiratory tract irritation (USEPA/NAC, 2003; Arts et. al., 2006a). A concentration of 1 ppm appears to be the approximate threshold for complaints of symptoms ranging from none to mild to moderate with no clear concentration-response relationship or increase in complaints among exposed subjects compared with controls. For example, a study in asthmatics (Harving et al., 1990) found no association between subjective ratings of sensory irritation and increasing formaldehyde exposures at concentrations of 0, 0.01, 0.1, and 0.69 ppm. USEPA/NAC (2003) identified 0.9 ppm as the highest exposure concentration at which the responses of subjects whose eyes were sensitive to formaldehyde were not significantly different from controls. Even at 3 ppm, however, the majority of subjects reported only mild (typically defined as present but not annoying) to moderate (annoying) irritation. In only one study, again in asthmatics at 3 ppm, did any subject rate the eye irritation as severe (1 of 180 subjects) (Sauder et al, 1987).

This same study (Sauder et al, 1987) illuminates why well conducted studies are necessary in order to properly understand and quantify the irritant properties of formaldehyde. In this study, 22% of subjects exposed to air containing no formaldehyde reported eye irritation, and 33% reported nose or throat irritation. Such a large incidence of false positive reporting would likely have an influence on any study for which it was not accounted.

Response 9:

The study mentioned in this comment by Sauder et al. (1987) had only 9 subjects, not 180 as indicated in this comment. Thus one subject with eye irritation out of nine is a much larger

proportion of the respondents. Nonetheless, due to the small study size, the results must be viewed with caution.

Comment 10:

Many of the controlled inhalation studies included potentially sensitive individuals. These studies either excluded less sensitive individuals (e.g., those without complaints of eye irritation at 1.3-2.2 ppm or smokers) or focused on potentially sensitive individuals (e.g., asthmatic individuals and those with formaldehyde-related contact dermatitis or previous formaldehyde sensitivity). As summarized by USEPA/NAC (2003), Bender (2002), and Paustenbach et al. (1997), the results of these studies indicate that sensitive individuals might experience eye irritation at 1 ppm. Below 3 ppm, the chemical appears to be rapidly eliminated in the upper airways, because asthmatics (who normally react to mid-and lower-respiratory airway irritants) engaging in moderate exercise showed no decrements in several pulmonary function parameters when exposed at concentrations up to 3 ppm. Thus, asthmatics exposed to airborne formaldehyde at exposure concentrations at or below 3 ppm do not appear to be at greater risk of suffering airway dysfunction than non-asthmatics. In addition, the short-term chamber studies indicate that adaptation or accommodation to irritation can develop over time (NRC 2004). These studies support that formaldehyde irritancy does not follow Haber's law (concentration x exposure time = response) for extrapolating between short-term and long-term time periods. Generally, concentrations that do not produce short-term sensory irritation also do not produce sensory irritation after repeated exposure. Consequently, conventional safety factors applied to a non-cancer risk assessment for formaldehyde are unnecessary.

Response 10:

The formaldehyde REL document summarizes some of the sensory irritation effects of formaldehyde. Sensory irritation is not considered to be the health effect of concern for the determination of the 8-hour or chronic noncancer REL, which are based on histological changes in the upper respiratory tract, not sensory responses. In determination of a chronic Reference Exposure Level (REL) for the noncancer effects of formaldehyde, irritation was not used as the endpoint of concern. Short-term experiments do not provide adequate information on long-term chronic effects of formaldehyde exposure. Sensory irritation and odor threshold, although important, are not relevant to OEHHA's derivation of the 8-hour (repeat exposure) or a chronic REL for formaldehyde (OEHHA, 2000).

The discussion of sensory irritation in the comments from the FCI revolves around articles developed for the purpose of evaluating and setting occupational standards of workers to avoid moderate eye irritation. Occupational standards are not relevant to community exposures due to the presence of children, the elderly, etc., in the general population. OEHHA agrees that sensory irritation is a sensitive endpoint. OEHHA is concerned with the protection of sensitive subpopulations, including children and asthmatics. Other studies have also reported complaints of irritation at doses less than 1 ppm. ATSDR (1999) reported at concentrations as low as 0.4 ppm sensory irritation was observed in humans. Pazdrak et al. (1993), Krakowiak et al. (1998), and Gorski et al (1992) all showed respiratory or irritative properties of formaldehyde at 0.4 ppm. Arts et al. (2006) states "In literature, a concentration as low as 0.24 ppm has been reported to be irritating to the respiratory tract in humans."

Most importantly, the threshold for changes in the nasal epithelium in workers exposed to formaldehyde appears to be lower than the alleged sensory threshold. Nasal epithelial damage occurs in long-term occupational exposures, and sensory irritation is not relevant to this endpoint. It should be noted that many irritants including formaldehyde are not only sensory irritants but also cause tissue damage. Sensory irritants can also cause irritation via other mechanisms and can damage tissue. Finally, formaldehyde is not purely a sensory irritant.

Comment 11:
Confounding Factors in Sensory Irritation Testing

There are several explanations for reported eye irritation levels by formaldehyde below 1.0 ppm, the primary one, however, is associated with the substance's odor. Formaldehyde has a pungent odor and the odor of formaldehyde is detected and/or recognized by most human beings at concentrations below 1.2 mg/m^3 (1 ppm) (IPCS 1989). In general, odor detection is not regarded as a toxicologically relevant endpoint -- annoyance does not represent a sensory or psychological effect, but rather a psychological discomfort from the presence and increasing concentration of an odor. (Arts et al. 2006b).

Foul odors are detected by both olfactory and trigeminal stimulation. The olfactory stimulation relays messages to the brain using the first cranial nerve for odor perception while trigeminal stimulation is responsible for sensing the ocular and nasal irritation of a chemical using the fifth cranial nerve. (Paustenbach and Gaffney 2006). In other words, olfactory receptors detect odor threshold while trigeminal nerve endings in the cornea and nasal mucosa signal sensory irritation thresholds in the eyes and upper respiratory tract, respectively. Olfactory receptors respond to chemical stimuli usually at lower concentrations and with greater selectivity than do the trigeminal endings and are responsible for the discrimination of different odorous substances. (Arts et al. 2006b). Although anatomically distinct, both pathways help people to distinguish and characterize inhaled air.

Studies have shown that even a pure odorous substance, lacking any trigeminal stimulation, elicited reports of sensory irritation. (van Thriel 2006). For the majority of chemicals, odor has a zero correlation with actual exposure risk, but odor may have a substantial correlation with perceived exposure risk. However, as Paustenbach and Gaffney (2006) note, "detection of odors by workers may tap into the person's aversions to unpleasant odors, in general." Because the vast majority of volatile chemicals stimulate the olfactory system at concentrations well below that at which they will elicit trigeminal activation, the evaluation of irritation from volatiles is often confounded by the perception of odor. (Arts et al. 2006b). Formaldehyde is not an irritant at its odor threshold; however, much of the public immediately perceives the substance and its odor as harmful, which strongly influences individuals to indicate irritation where only odor exists. Thus, the results of measurements of sensory irritation can strongly be biased by subjective feelings and interpretations, in many instances caused by the odor of the compound. Therefore, the perception of odor intensity is an important factor that must be considered when evaluating a substance for an occupational exposure limit, especially substances that like formaldehyde have odors perceived as unpleasant.

Response 11:

OEHHA recognizes the perception of foul odor as an "effect". Detection of foul odor may lead to other irritant effects even if the discomfort is psychologically-induced. In addition, pathophysiological effects have been seen in response to odor (e.g. by pregnant women and for other chemicals like H_2S). OEHHA does not disagree that odor perception is distinct from trigeminal nerve stimulation. OEHHA is not using odor perception or odor threshold to set a chronic Reference Exposure Level.

Occupational standards are not used to set standards for the general public, which includes infants and children, the elderly, pregnant women, ill people and more sensitive individuals. Occupational standards are recognized to protect some but not all workers and allow higher risks than environmental standards for the general public. Also, in an occupational setting, workers may be less likely to complain and may be "acclimated" to odor or irritation from low doses (1 ppm or less) of formaldehyde.

OEHHA recognizes these previous reviews have been performed and have taken into account information found therein. However, OEHHA relies on primary sources of peer-reviewed literature in its noncancer health risk assessments.

Previous Expert Evaluations of Formaldehyde and Sensory Irritation

Several expert reviews have been conducted of the formaldehyde literature relating to sensory irritation. Based on the reviews by the National Academy of Sciences' National Research Council (NRC 2004), Arts et al. (2006), Bender (2002) and Paustenbach et al. (1997), the weight of the scientific evidence demonstrates that the threshold for formaldehyde sensory irritation of the most sensitive endpoint (i.e., eye and respiratory tract irritation) is in the range of 0.75 to 1 ppm.

Comment 12:

NRC (2004)

In reviewing the exposure of U.S. Navy personnel in submarines to several different contaminants, a subcommittee of the NRC developed exposure guidance levels for formaldehyde (assuming exposure 24 hours per day for several weeks at a time). The report contains a thorough discussion of the literature on the relevant epidemiologic and toxicologic studies on formaldehyde, and concludes:

> A concentration of 1 ppm appears to be the approximate threshold between complaints of symptoms ranging from none to mild to moderate with no clear concentration-response relationship or increase in complaints among exposed subjects compared with controls (subjects exposed to

clean air) and definite symptoms of discomfort in a number of exposed subjects.[10]

Response 12:

With regards to the National Research Council (NRC) paper mentioned in the above comment, navy personnel are less likely to complain and may be able to withstand more odor or irritation because of their training, and become acclimated, especially those trained to spend months at a time on submarines. Also, Navy personnel on submarines would be of much better health than a "normal" person and therefore are not representative of the general population. The studies mentioned above are of occupational exposure and do not include infants, children, and pregnant women. Finally, as noted above, the major concern from a repeated or chornic exposure perspective, is the nasal epithelial damage seen in workers. This is the basis for our 8-hour and chronic RELs.

Comment 13:

Arts et al. (2006a)

Arts et al. (2006a) evaluated literature related to critical health effects of formaldehyde exposure including sensory irritation and the potential to induce tumors in the upper respiratory tract. The authors reviewed the subjectively measured sensory irritation threshold levels in humans and compared this with findings obtained in animal experiments. In addition, a benchmark dose (BMD) analysis of sensory irritation was used to estimate response incidences at different formaldehyde concentrations. The BMD method used by the authors takes all individual data into account by means of a curve based on all the data points.[11] Arts et al. concluded that:

- when minimal/mild/slight irritation, which is still not annoying, is taken as a cut off level, eye and nasal irritation were found at formaldehyde levels of ≥1 and ≥2 ppm,

- the minimal/mild/slight irritation level would be ≥3 ppm formaldehyde for throat irritation, whereas levels of up to 3 ppm did not result in dyspnoea (chest tightness/discomfort) or cough.[12]

The authors were sensitive to the challenge of setting appropriate exposure levels based on sensory irritation. Because human perception of sensory irritation can be influenced strongly by subjective feelings and interpretations, the authors contend that it would be better to base the sensory irritation threshold on objective measurements. In the authors' view, the only study that

[10] National Research Council (2004) Emergency and Continuous Exposure Guidance Levels for Selected Submarine Contaminants, Subcommittee on Emergency and Continuous Exposure Guidance Levels for Selected Submarine Contaminants, Committee on Toxicology, at 89.

[11] Arts et al. (2006a) at 15.

[12] *Id*. at 18-19 (references omitted).

reported objectively measured eye irritation (but not nasal irritation), viz. an increase in eye blinking frequency at a concentration of 1.7 ppm formaldehyde (Weber-Tschopp et al., 1977), is in line with minimal/mild/slight eye irritation reported at levels of 1 ppm and higher. It was noted that the increase in eye blinking frequency was not doubled yet at 3.2 ppm. (Weber-Tschopp et al., 1977).

Collectively, Arts et al.'s review leads to the conclusion that: "Sensory irritation is first observed at levels of 1 ppm and higher. From both human and animal studies it was concluded that at airborne levels for which the prevalence of sensory irritation is minimal both in incidence and degree (i.e. < 1 ppm), risks of respiratory tract cancer are considered to be negligibly low."[13]

Response 13:

Arts et al. (2006) were attempting to evaluate a level appropriate to avoid undue irritation in the workplace. The conclusions by Arts et al. (2006) are based on only one paper found in the literature, that used an objective endpoint (eye blinking frequency). This one study (Weber-Tschopp et al. (1977)) had the limitation that one ppm was the lowest dose used. Therefore, a conclusion that sensory irritation was first observed at levels of 1 ppm and higher is misleading if lower concentrations were not tested. In addition, Arts et al. (2006) states, "…there is not a large discrepancy between subjectively reported symptoms and objectively measured nasal sensory irritation." In any event, the observation of sensory irritation at these levels is not particularly relevant to long-term exposure given that hyperplasia has been reported in exposed workers at about 0.26 mg/m^3 (0.2 ppm) in studies by Wilhelmsson and Holmstrom (1992), and Edling et al. (1988). This effect is the basis of the OEHHA chronic REL.

Comment 14:

Bender (2002)

Bender (2002) reviewed whether human sensory irritation data found in controlled/chamber studies and workplace studies are sufficiently robust for use in establishing a Reference Concentration for formaldehyde. Bender (2002) determined that chamber studies provided the highest quality data for determining the presence of eye, nose or throat irritation at a known level of formaldehyde. Chamber studies show that individuals began to sense eye irritation at about 0.5 ppm formaldehyde; 5 to 20 percent reported eye irritation at about 0.5 to 1 ppm, and greater certainty for sensory irritation appeared at 1 ppm or greater.[14]

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[13] *Id.* at 2. The Arts et al. analysis also confirms that anticipated exposure levels will not create the biological conditions or events triggering chronic risk concerns. "Overall, an exposure level of 1 ppm did not induce respiratory epithelial hyper/metaplasia, whereas levels of 2-3 ppm induced slight respiratory epithelial hyper/metaplasia, and levels of about 6 ppm and higher induced extensive hyper/metaplasia, necrosis, and severe rhinitis. An increased incidence of nasal cell carcinomas was seen from about 10 ppm, concomitant with clear cytotoxic effects. IARC (2004) concluded that there is sufficient evidence in experimental animals for the carcinogenicity of formaldehyde." Manuscript at 14.

[14] Bender (2002) at 13.

Bender et al., also evaluated reports of eye irritation among controlled studies, and found that it is not unusual to have a 20 to 30 percent response rate for eye, nose, or throat irritation associated with controls. Bender, et al., concluded that sensory irritation at levels below 1 ppm is often difficult to distinguish from effects that occurred in controls.[15]

Response 14:

With regards to the comments on chamber studies mentioned in the Bender review section above, it should be noted that chamber studies typically involve small numbers of healthy individuals and so won't detect effects on sensitive members of the population. In addition, chamber studies are insensitive due to small sample size, population selection (not necessarily sensitive people in the sample), inability to evaluate prior and concurrent exposure which is important in a community setting, and inability to evaluate longer term exposures. Kulle et al. (1987), the basis of the acute REL, reported a LOAEL of 1 ppm. OEHHA applied uncertainty factors to the benchmark concentration to account for the potential sensitivity of children. OEHHA is aware of the difficulties in evaluating eye and nasal irritation, including a high background rate in symptom reporting.

Comment 15:

Paustenbach et al. (1997)

Paustenbach et al. (1997) represents the results of deliberations of a panel of experts convened to review the literature on sensory irritation. The expert panel reviewed approximately 150 published scientific articles and concluded that the most sensitive adverse effect of formaldehyde is eye irritation. Eye irritation "does not become significant until a concentration of at least 1.0 ppm is reached, and, based on most studies, for most people this level of irritation rapidly subsides."[16] Moderate to severe eye, nose, and throat irritation does not occur until airborne concentrations exceed 2.0 to 3.0 ppm.[17]

According to the expert panel, the weight of the evidence showed that reports of irritation below 0.3 to 0.5 ppm formaldehyde were too unreliable to attribute the findings solely to formaldehyde. Specifically, response rates below 20 percent were assumed to be too near the background level of irritation among the general population to be able to attribute that level of response to exposure to a specific contaminant.[18] In response to studies that showed irritation response at concentrations below 0.1 ppm, the panel explained: "it is likely that this level of response was

[15] *Id.*

[16] Paustenbach et al. (1997) at 252.

[17] *Id.* at 218.

[18] *Id.* at 251.

attributable to other environmental factors, the background incidence of eye irritation, self-selection bias, or the effects of interviewer interaction."[19]

IRSST (2006)

The Québec Institute of Research Robert-Sauvé en santé et en sécurité du travail (IRSST) recently completed a thorough evaluation on the *Impacts of a Lowering of the Permissible Exposure Value to Formaldehyde: Impacts of Formaldehyde Exposure on Health.*[20] IRSST is a private, non-profit scientific research organization known for the quality of its work and the expertise of its personnel. The Board of Directors is composed of an equal number of trade union and employers' representatives.

With respect to the issue of sensory irritation, this evaluation critically considered all available studies with the notable inclusion of a rigorous dose-response analysis of the available data. Unlike other evaluations, based on pre-established criteria, this analysis considered sensory irritation effects (e.g., eye irritation, moderate and severe, and moderate nose and throat irritation), the percentage of workers who might experience such effects, and most importantly, the associated dose-response relationships.

The relationship between acute formaldehyde exposure and the appearance of effects was established based on the collection of all rough data from each of the studies considered to have a degree of confidence moderately high to high. Hence, these studies are all led in a controlled setting. Moreover, the effects selected for the establishment of a dose-response relationship are the irritating effects to the eyes and airway mucosa (nose and throat) as well as perception of odor. These effects are most frequently reported following an acute exposure to formaldehyde suggesting that they are the critical effects (those that appear with the lowest concentrations).

For each of the controlled studies, the number of subjects presenting irritating effects, according to the class of exposure and the severity of the effect, was listed. The degree of exposure was fractioned into six distinct classes: from 0 to <0.3 ppm, from 0.3 to <0.75 ppm, from 0.75 to <1.0 ppm, from 1.0 to <2.0 ppm, from 2.0 to <3.0 ppm, and >3.0 ppm (which in fact combined the exposures between 3.0 and 4.0 ppm).[21]

By combining the data from the different controlled studies, a global dose-response relationship was established. More specifically, the total number and the proportion of subjects presenting irritating effects by type of effects, severity of effects and class of exposure were compiled in the form of a table by adding the numbers of the different studies. This data allowed the creation of

[19] *Id.* at 250-51.

[20] The report is available on the IRSST website at http://www.irsst.qc.ca.

[21] *Id.* section 4.1.1.2.

dose-response curves where the background noise value, that is to say the frequency of irritations in the absence of exposure, was subtracted.[22]

The conclusions of the IRSST review are noteworthy.

> Our analysis indicates that, for concentrations less than 0.75 ppm, the frequency of irritation in workers exposed to formaldehyde was about the same as the one observed in individuals without occupational exposure. This means that appearance of irritation at such concentrations can hardly be associated with occupational exposure to formaldehyde. For concentrations between 0.75 and 3 ppm, the estimated proportion of workers who may experience moderate irritating effects to the eyes, nose, and throat, attributed to formaldehyde is between 1.6 and 14.9%.[23]

Many of the controlled inhalation studies included potentially sensitive individuals. These studies either excluded less sensitive individuals (e.g., those without complaints of eye irritation at 1.3-2.2 ppm or smokers) or focused on potentially sensitive individuals (e.g., asthmatic individuals and those with formaldehyde-related contact dermatitis or previous formaldehyde sensitivity). As summarized by USEPA/NAC (2003), Bender (2002), and Paustenbach et al. (1997), the results of these studies indicate that sensitive individuals might experience eye irritation at 1 ppm. Below 3 ppm, the chemical appears to be rapidly eliminated in the upper airways, because asthmatics (who normally react to mid-and lower-respiratory airway irritants) engaging in moderate exercise showed no decrements in several pulmonary function parameters when exposed at concentrations up to 3 ppm. Thus, asthmatics exposed to airborne formaldehyde at exposure concentrations at or below 3 ppm do not appear to be at greater risk of suffering airway dysfunction than non-asthmatics. In addition, the short-term chamber studies indicate that adaptation or accommodation to irritation can develop over time (NAS, 2004). These studies support that formaldehyde irritancy does not follow Haber's law (concentration x exposure time = response) for extrapolating between short-term and long-term time periods. Generally, concentrations that do not produce short-term sensory irritation also do not produce sensory irritation after repeated exposure. Consequently, conventional safety factors applied to a non-cancer risk assessment for formaldehyde are unnecessary.

Response 15:

The purpose of the analyses by Paustenbach et al. (1997) and IRSST (2006) was to set occupational exposure limits based on sensory irritation. OEHHA seeks to protect the general

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[22] *Id.* section 4.1.1.3.

[23] *Id.* section 7.1. IRSST (2006)(section 6.1.4) also compared its review to the analysis in Paustenbach (1997): "In addition, not only were controlled studies considered in the determination of the dose-response relationship, but studies showing a lower confidence level were also considered, that is, studies performed in the workplace. The background noise in the general population was not subtracted, and the irritation classification was not based on the degree of severity of the effect (mild, moderate, or severe irritation). In spite of a methodology, which was different from the one used in this study, it was concluded that a ceiling value of 1 ppm for 15 minutes was appropriate to prevent moderate, although transitory, eye irritation. The authors [Paustenbach (1997)] also stated that at such concentrations, formaldehyde should not cause eye irritation in at least 75% of workers and possibly up to 95%."

public including sensitive subpopulations, and occupational standards are not appropriate to use for the general public. Further, the FCI comments footnote 24 states "Paustenbach notes that 1 ppm for 15 minutes was meant to prevent moderate eye irritation in 75% of workers". This would be inappropriate to apply to the general population either for acute or longer term exposures.

Comment 16:

NICNAS (2006)

NICNAS (2006) is an assessment was carried out under the Australian National Industrial Chemicals Notification and Assessment Scheme (NICNAS). The principal aim of NICNAS is to aid in the protection of people at work, the public and the environment from the harmful effects of industrial chemicals. NICNAS assessments are carried out in conjunction with the Australian Government Department of the Environment and Heritage, which carries out the environmental assessment for NICNAS.

Based on a review of the literature, NICNAS (2006) (page V) concluded that: "The lowest-observed-effect level (LOEL) for sensory irritation in humans is 0.5 ppm." The report's discussion of sensory irritation (NICNAS at 72-74) speaks for itself, and the relevant excerpts follow.

> Sensory irritation is the result of the chemical stimulating the trigeminal nerve endings in the cornea and nasal mucosa, which evokes a stinging or burning sensation in the eyes and upper respiratory tract (nose and throat). This is a receptor mediated mode of action and occurs at relatively low concentrations. Sensory irritation is different to eye and skin irritation/corrosivity used for hazard classification (Section 12.2) and also different from the irritation leading to cytoxicity, hyperplasia and nasal tumours (Section 10.4.1). These latter examples are a result of physical damage to the cells, whereas sensory irritation is a nerve response.
>
> Formaldehyde exposure has long been associated with irritation to the eyes and upper respiratory tract. Repeated complaints, such as sore eyes and throat by embalmers were reported in the NICNAS survey.
>
> In more recent years, chamber studies have investigated sensory irritation following short-term exposures to known low levels of gaseous formaldehyde.
>
> In chamber studies in healthy and asthmatic volunteers, mild to moderate eye irritation was self-reported following exposure to formaldehyde levels ranging from 0.25 to 3 ppm (0.3 to 3.6 mg/m3) for up to 5 hours, though exposures were generally < 3 hours. Overall, the data from these studies indicate that eye irritation is a more sensitive parameter than nose and throat irritation which was generally self-reported at concentrations > 1 ppm (Weber-Tscopp et al., 1977; Andersen & Molhave, 1983; Bender et al., 1983; Day et al., 1984; Schachter et al., 1986; 1987; Sauder et al., 1986; 1987; Green et al., 1987; 1989; Kulle et al., 1987; Kulle, 1993; Witek et al., 1987). A summary of these studies can be found in Table 11.1.

It should be noted that a study by Pazdrak et al. (1993) is not included in Table 11.1 because of major methodological shortcomings (e.g. exposures could not be verified as information was not provided regarding the techniques used to generate the aerosol or the methods used to measure formaldehyde). A study by Krakowiak et al. (1998) also has methodological shortcomings and is also not included.

Sensory irritation due to exposure to formaldehyde has rapid onset (Sauder et al. 1987, Yang et al. 2001) and the intensity of effect does not appear to significantly increase with longer exposures (Sauder et al. 1987). This is in accord with the theoretical considerations of sensory irritation where the intensity of response is dependent on the concentration of the substance and not the duration of exposure.

A study is available where exposure to formaldehyde was through modified eye goggles (Yang et al., 2001). Eight volunteers were exposed to 0, 1.65, 2.99 or 4.31 ppm formaldehyde for 5 minutes and eye irritation was self-reported. Individual scores were not reported. Although the higher formaldehyde concentrations resulted in greater eye irritation scores, compared to control exposures irritancy scores were only statistically significant at 1.65 and 4.31 ppm, and only 1.5, 2.5 and 3.0 minutes after the onset of exposure. A study is available where exposure was via a facemask (Reed & Frigas, 1984). Thirteen subjects who had reported respiratory symptoms to previous exposures of formaldehyde were exposed for 20 minutes to concentrations up to 3 ppm (3.6 mg/m3) formaldehyde. No significant effect was seen on pulmonary function, while self-reports of eye, nose and throat irritation occurred as frequently with clean air as with formaldehyde. . . . . .

Therefore, although formaldehyde is a known eye and upper respiratory tract irritant in humans, the limitations of the available data and subjective nature of sensory irritation do not allow identification of a definitive no-observed-effect level (NOEL). The data from chamber studies demonstrate that the sensory irritation responses at levels of $\geq$ 1 ppm (1.2 mg/m3) can definitely be attributed to formaldehyde. Some individuals begin to sense irritation from 0.5 ppm (0.6 mg/m3), although the response rate is often similar to that reported in controls. Although there is limited evidence that some individuals report sensory irritation at concentrations as low as 0.25 ppm (0.3 mg/m3) the data are very unreliable. Therefore, the LOEL is considered to be 0.5 ppm.

Response 16:

The LOEL of 0.5 ppm mentioned above is half the LOAEL, and equal to the NOAEL, in the study by Kulle et al. (1987) based on sensory irritation. We utilized a BMD approach with data from this study to calculate an acute REL. It is approximately twice the LOAEL (0.21 ppm) for nasal histopathology and lower airway discomfort used in the chronic REL. Thus, the conclusions of the NICNAS report appear to be supportive of the data used in the REL.

Comment 17:
Lang et al. (2008)

The most recent study relevant to sensory irritation is Lang et al. (2008) "Formaldehyde and chemosensory irritation in humans: A controlled human exposure study." According to the authors:

> *Objectives*: The objective of this study was to examine the possible occurrence of sensory irritation and subjective symptoms in human volunteers exposed to formaldehyde concentrations relevant to the workplace. The set up of the study included formaldehyde exposures with and without peaks, the presence and absence of a masking agent, and evaluation of the influence of personality factors.
>
> *Methods*: Testing was conducted in 21 healthy volunteers (11 males and 10 females) over a 10-week period using a repeated measures design. Each subject was exposed for 4 h to each of the 10 exposure conditions on 10 consecutive working days. The 2-week exposure sequences were randomized, and the exposure to formaldehyde and the effect measurements were conducted in a double-blind fashion. During 4 of the 10 exposure sessions, 12–16 ppm ethyl acetate (EA) was used as a 'masking agent' for formaldehyde exposure. Measurements consisted of conjunctival redness, blinking frequency, nasal flow and resistance, pulmonary function, and reaction times. Also subjective ratings of discomfort as well as the influence of personality factors on the subjective scoring were examined. These were carried out pre-, during and/or post-exposure, and were used to evaluate the possible irritating effects of formaldehyde at these concentrations. Results: The results indicated no significant treatment effects on nasal flow and resistance, pulmonary function, and reaction times. Blinking frequency and conjunctival redness, ranging from slight to moderate, were significantly increased by short-term peak exposures of 1.0 ppm that occurred at a baseline exposure of 0.5 ppm formaldehyde. Results of the subjective ratings indicated eye and olfactory symptoms at concentrations as low as 0.3 ppm. Nasal irritation was reported at concentration levels of 0.5 ppm plus peaks of 1.0 ppm as well as at levels of 0.3 and 0.5 ppm with co-exposure to EA. However, exposure to EA only was also perceived as irritating. In addition, volunteers who rated their personality as 'anxious' tended to report complaints at a higher intensity. When 'negative affectivity' was used as covariate, the level of 0.3 ppm was no longer an effect level but 0.5 ppm with peaks of 1.0 ppm was. Increased symptom scores were reversed 16 h after the end of the exposures.
>
> *Conclusions*: The results of the present study indicated eye irritation as the most sensitive parameter. Minimal objective eye irritation was observed at a level of 0.5 ppm with peaks of 1 ppm. The subjective complaints of ocular and nasal irritation noted at lower levels were not paralleled by objective measurements of eye and nasal irritation and were strongly influenced by personality factors and smell. It was concluded that the no-observed-effect level for subjective and objective eye irritation due to formaldehyde exposure was 0.5 ppm in case of a constant exposure level and 0.3 ppm with peaks of 0.6 ppm in case of short-term peak exposures.

The study protocols in Lang et al. (2008) address the weaknesses in prior studies and are consistent with contemporary best practices. Thus, Lang et al. (2008) helps clarify the appropriate interpretation of the prior literature on the sensory irritation of formaldehyde and validates prior expert reviews that place the sensory irritation level for formaldehyde in the 0.5 to 1.0 ppm range. As Lang et al. (2008) conclude:

> Objective measurements of functional nasal parameters at exposure levels up to 0.5 ppm (with and without peaks) did not result in any significant changes which was in line with observations by Kulle et al. (1987) and Kulle (1993). They found an increase in nasal resistance at a concentration of 3 ppm but not at 1 or 2 ppm. Subjective measurements revealed that nasal irritation was reported to be significantly higher in subjects exposed to 0.5 ppm with peaks of 1.0 ppm with or without EA. At lower concentrations, subjects could not differentiate between the irritation caused by formaldehyde and the perception of the EA odour.

Response 17:

OEHHA has read the Lang et al. (2008) manuscript. It should be noted that Lang et al. (2008) report sensory irritation at 0.5 to 1.0 ppm. Thus, this is consistent with the Kulle et al (1987) report which is the basis of the acute REL.

Comment 18:
Formaldehyde in Nature

Formaldehyde is one of the simplest biological forms of carbon. Even the most primitive organisms rely on formaldehyde as a one-carbon building block for the synthesis of more complex molecules. As a result of its importance in various metabolic processes, formaldehyde is naturally present in the human body with concentrations of approximately 1-2 parts per million (ppm) in the blood. Formaldehyde is exhaled in the breath, with studies suggesting that breath levels may range from the low parts per billion (1.2-72.7 ppb) to 0.3–1.2 ppm (Moser et al. 2005; Ebeler et al. 1997).

Due to the highly efficient activity of a variety of aldehyde dehydrogenase (ADH) enzyme systems, formaldehyde is rapidly metabolized. For example, blood was collected immediately following exposure of F-344 rats to 14.4 parts per million (ppm) of formaldehyde for 2 hours. Blood from eight unexposed rats served as controls. Analysis showed formaldehyde concentrations of 2.24 and 2.25 μg/g blood in exposed and controls, respectively (Heck et al. 1985). Formaldehyde concentrations in human venous blood from four males and two females were determined by analyzing blood samples collected before and after exposure to 1.9 ppm of formaldehyde for 40 minutes. Average formaldehyde concentrations before and after exposure were 2.61 and 2.77 μg/g blood, respectively. In neither rats nor humans was there a statistically significant effect of formaldehyde exposure on the average concentrations in the blood. In a similar study, three rhesus monkeys were exposed to formaldehyde at 6 ppm (6 hours/day, 5 days/week for 4 weeks) and the formaldehyde concentration in the blood measured by gas chromatography - mass spectrometry (GC-MS). The formaldehyde concentrations immediately after the final exposure in the three exposed and three unexposed animals were 1.84 and 2.42 μg/g blood, respectively. These results demonstrate that subchronic inhalation exposure of non-

human primates to formaldehyde has no significant effect on the concentration in the blood, and that the average concentration of formaldehyde in the blood of monkeys is similar to that observed in human studies (Casanova et al. 1988). California risk assessments should recognize and account for the status of substances that the body naturally generates and for which there are highly efficient detoxification pathways, in contrast to substances for which metabolic detoxification pathways are absent or limited.

Once formaldehyde enters the environment, it begins to break down through natural processes and does not persist or bioaccumulate. Chenier (2003). From a regulatory and public policy perspective, it always is necessary to differentiate and recognize the relative importance of substances that are naturally occurring, biogenic chemical components, especially those that have multiple and highly efficient pathways existing for their conversion into a usable source. Such is the case with formaldehyde and its conversion to a carbon source, formate. Formaldehyde's role in our environment is vastly different from substances that have no roles in normal metabolism and physiology. For this reason, OEHHA should not apply any risk assessment or REL derivation methodology that ignores or conflicts with the realities of the biological role of formaldehyde and the biological systems within which formaldehyde may be present.

Response 18:

Many normal products of metabolism in plants fungi, and animals are in fact toxic – being natural does not mean being nontoxic or even less toxic than synthetic chemicals. Furthermore, many toxic chemicals are also constituents of living systems including nickel, a known human carcinogen is also an essential trace nutrient. Formaldehyde is indeed a natural constituent found in cells produced during normal human intermediary metabolism, and as a result of certain disease processes such as lipid peroxidation. But formaldehyde is still a carcinogen and additional exposure should be avoided. Organisms have evolved ways to handle formaldehyde produced during intermediary metabolism to control the reactive compound in our cells. However, these protective mechanisms may be overwhelmed with exogenous formaldehyde from the air we breathe. In addition, it is recognized that some human diseases such as cancer may result from our "carbonyl" body burden of which formaldehyde is a component. It should be noted that there are data to suggest elevated formaldehyde body burden due to human disease states such as cancer and diabetes.

Formaldehyde in cells is mostly bound to a cofactor or enzyme during intermediary metabolism and is not free in the cell. Endogenously produced formaldehyde is in the aqueous phase and therefore hydrated (demonstrably less harmful than inhaled from external sources, although not necessarily harmless). Finally, most recent and reliable methodology indicates formaldehyde levels in breath in the low ppb range in healthy people: higher levels appear to be associated with disease states, such as inflammation or cancer which enhance lipid peroxidation. The values from Moser (1.2 - 72.7 ppb; median 4.26 ppb) for human breath are compared with values ARB has for conventional homes of 13.9 ppb on average, with the maximum >200 ppb. (Moser et al., 2005).

CONCLUSION

The comments and analysis provided by FCI are intended to support OEHHA's efforts to ensure that its decision rests on the best available science and supporting studies conducted in accordance with sound and objective scientific practices, including, when available, peer reviewed science and supporting studies. While FCI and its members have prepared these comments based on our good faith understanding of the toxicological science of formaldehyde, we wish to clarify what might be misinterpreted as a conflict between our comments and our actions. On one hand, FCI and its members are committed to improving the state of the art with regard to formaldehyde toxicology and risk assessment techniques on which to base the regulation of formaldehyde and formaldehyde products. It is from that science perspective that these comments were prepared.

From a product stewardship perspective, FCI recognizes the general and continuing goal of reduced exposure. From that perspective, we take some pride in the great strides that have been made since consumer complaints in the early and mid-1980's when levels of formaldehyde were much higher than they are today. Over the last 20 years, and mostly due to voluntary industry efforts, resin formulations and wood product manufacturing techniques have been modified to reduce emission levels in the finished product. In 1997, the US Consumer Product Safety Commission (CPSC) found that "[m]anufacturers have reduced formaldehyde emissions from pressed wood products by 80-90% from the levels of the 1980's." As a result of these various product modifications and reduction of formaldehyde emissions, consumer complaints have largely ceased. We believe that OEHHA's fundamental goals are aligned with those of FCI. In the case of the proposed guidelines, FCI has concluded that the science does not support the proposed governmental action.

FCI and its members have continued to invest in toxicological research to support the scientific community's efforts to better understand the toxicological properties of formaldehyde and refine risk assessment methodologies that protect human health and the environment with increasing levels of certainty. While new studies may advance our understanding, FCI recognizes that new studies may also raise new issues or prompt the re-examination of existing data. FCI has carefully reviewed the entire universe of scientific literature on formaldehyde, including recently published studies and reviews. In light of the overall state of the literature as supported by an array of expert reviewers, the RELs for formaldehyde should be revised.

The Formaldehyde Council and its members would be happy to discuss this matter or provide additional analysis if it would assist OEHHA.

Response:

Thank you for your review and comments.

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Comments of Patrick A. Schanen, on behalf of the Los Angeles Unified School District.

Comment 1:

We are concerned that the toxicity of diesel exhaust was not addressed in this document. In our experience, diesel exhaust is a common risk driver for cancer when conducting Air Quality Health Risk Assessments (HRA's) for new school sites. However, it is exceedingly rare that diesel exhaust (expressed as Diesel Particulate Matter [DPM]) exceeds the significance threshold for non-carcinogenic risks. It should be noted that even for the recent HRA's conducted by the California Air Resources Board for several rail yards in the Los Angeles area, the significance threshold for non-carcinogenic risks was rarely exceeded. It is surprising that DPM was not updated in the proposed TSD as DPM is considered a high-priority, Tier 1 compound.' This is especially concerning considering that all six Toxic Air Contaminants with updated REL's in this document are components of DPM. We recommend that the TSD be revised to consider updating the toxicity criteria for diesel exhaust.

Response

The fundamental purpose of the current revision process and public comment period is to address revision of the technical support document describing the derivation of non-cancer health protective values (Reference Exposure Levels). We have included draft RELs for six chemicals (five of which are SB25 priority compounds in Tier 1 or Tier 2) in the first instance as examples and test cases for the proposed new assessment guidelines, although these also serve the additional purpose of updating these RELS in accordance with the SB25 mandate. Any other RELs generated at this time or subsequently will be added as they are approved: the technical support document has been deliberately structured so these may be added to the document appendices without revision of the main document. We are well aware of the concerns about the non-cancer effects of diesel exhaust particulate. These are the subject of ongoing study by OEHHA staff under the Toxic Air Contaminants program, the Air Toxics Hot Spots programs, and the Criteria Air Pollutants program. However, this very extensive project cannot be completed within the timeframe for revision of the Hot Spots risk assessment guidelines. We are currently working on addressing new information on diesel exhaust particulate matter.

Comment 2:

We support the inclusion of asthma as a toxic endpoint when establishing REL's as it is estimated that at least 63,000 of our students suffer from asthma. We also support the adoption of an eight-hour REL classification which will help to assess health risks for school-based populations. However we note that clarification might be necessary to assess how to apply these REL's to the daily exposure durations greater than eight hours called for by OEHHA guidance for school sites.

Response:

Thank you for your support of our efforts to include consideration of asthma, which we identified as a critical endpoint for children's health in the SB25 prioritization of Toxic Air Contaminants which OEHHA published in 2001. The application of 8-hour RELs and related exposure assessment matters will be addressed in the forthcoming revision of the Part IV (Exposure Assessment and Stochastic Analysis) technical support document.

Comment 3:

In sum, we strongly recommend prompt adoption of health protective REL's for emissions from mobile sources such as diesel exhaust, and generally support the proposed new methodology for developing and modifying REL's.

Response:

Thank you for your support. We look forward to your further input as we continue to develop RELs and other health standards which are protective of children's health, including updates to our consideration of diesel exhaust in due course.

Comments of Carri M. Matsumoto, on behalf of the Long Beach Unified School District.

Comment 1:

The LBUSD requests that OEHHA explain the reason diesel particulate matter was not 9among the initial group of six TACs for which updated RELs were reported in the revised TSD. The school district further requests that OEHHA discuss whether the agency has a priority scheme or schedule for developing an updated REL for diesel particulate matter. (The commenter also provides an extended discussion of their concerns about non-cancer health impacts of diesel exhaust particulate matter and related mobile source related pollutants, and the specific reasons why the Long Beach Unified School District regards these of particular importance to their operations and the community which they serve.)

Response

OEHHA will not be providing a detailed discussion of the materials presented at this point since this comment is not responsive to the request for comment on the technical support document and six specific RELs: other pollutants will be considered later. We included the six sample RELs (five of which are SB25 priority compounds in Tier 1 or Tier 2) in the first instance as examples and test cases for the proposed new assessment guidelines, although these also serve the additional purpose of updating these RELs in accordance with the SB25 mandate.

However, OEHHA is well aware of the justified concerns of LBUSD and other impacted organizations and community members, and is already engaged in the evaluation of non-cancer health effects of diesel exhaust particulate matter and related mobile source derived pollutants. These are the subject of ongoing study by OEHHA staff under the Toxic Air Contaminants program, the Air Toxics Hot Spots programs, and the Criteria Air Pollutants program. However, this is a very large undertaking, which cannot be addressed within the time frame of the guidelines revision effort. We are currently working on addressing new information on diesel exhaust particulate matter. The materials provided by LBUSD will be included in the ongoing consideration of these issues by OEHHA scientists.

Comment 2:

The LBUSD requests that OEHHA indicate whether or not, and how, UFP are/will be addressed in the REL development process.

Response

OEHHA is including consideration of ultra-fine particulate material in its ongoing evaluation of mobile source derived pollutants. It has not been determined at this point whether this will result in determination of RELs for use in the Air Toxics Hot Spots program, or development of health effects assessments within the framework of the Toxic Air Contaminants or Ambient Air

Quality Standards (criteria pollutants) programs. This will be determined in discussion with the California Air Resources Board.

Comment 3:

In summary, LBUSD reiterates its general support for the important initiative described in the revised TSD to develop RELs that reflect child-specific responses to environmental contaminants. We believe that the final TSD needs to expeditiously and adequately address diesel particulate matter (as well as ultra-fine particles) and, thereby, allow accurate assessment and effective mitigation of the corresponding impacts to schools and school children. We encourage you to prioritize your efforts to ensure development of RELs for emissions from Goods Movement-related activities - especially diesel particulate matter -- receives the highest level of consideration.

Response

OEHHA thanks LBUSD for their support of the effort to update the REL development process to include explicit consideration of children's health. The methodological guidance given in the main section of the technical support document is separate from individual RELS developed using these guidelines: the TSD has been deliberately structured so these may be added to the document appendices without revision of the main document. Any RELs generated at this time or subsequently will be added as they are approved. Prioritization for REL development is determined by OEHHA in consultation with the California Air Resources Board and local air districts: there are a number of critical issues currently demanding OEHHA's attention. As noted above in our response to Comment 2, OEHHA is already engaged in an ongoing effort to update the health risk assessment of mobile source derived pollutants. This includes participation in the current initiatives to evaluate risks and develop control strategies for pollution related to goods movement. However, this very extensive project cannot be completed within the timeframe for revision of the Hot Spots risk assessment guidelines.

Comment of Larry Dykhuis on behalf of Herman Miller, Inc.

Comment 1

Since I am not a toxicologist I can not provide comment specifically to improving the methodology. I can only look at the resultant REL's and offer some observations. My observations are related to one REL in particular, the 8 hour REL for formaldehyde in comparison to the Acute and Chronic REL.

It would seem that an 8 hour REL should be closer to the acute REL, which is intended to prevent effects at 30 min or 1 hour, than to the chronic REL which is intended to prevent effects over 10-30 years. Yet the proposed 8 hour REL is exactly the same as the chronic REL. This is apparently due to using the same health study as the basis for both the 8 hour and chronic REL, and also applying the same uncertainty factors. This was a chronic study so a question can be raised about the applicability of the chosen study for determining an 8 hour REL.

Response

The critical feature of the 8-hour REL in this case is that the 8-hour exposure is potentially repeatable on an occasional or ongoing basis, whereas the acute REL is designed to address an exceptional maximum (during normal operation – this is not a disaster response standard). Because of this, the sensitization which is the probable basis of the chronic response may occur in the 8-hour REL scenario: it appears that the sensitive state may be established after one or only a few short-term exposures. Once established, the dose-response for adverse respiratory effects is not particularly time-dependent, so in this case, exceptionally, the chronic and 8-hour REL and exactly the same.

Comment 2

I have other details about the development of formaldehyde REL that I have questions about but the above comment is the crux of my observation. I would be happy to discuss more details if you desire. The other items relate to the selection of uncertainty factors, using the control group exposure as the "safe" exposure level, and if the REL's from this methodology are only properly applied to "infants, children and other sensitive subpopulations," and if so how would OEHHA propose to limit their use.

Response

1. *We intend that the basis of the selected uncertainty factors should be clear to the reader of the REL summaries, and will review these to determine whether clarification is needed.*

2. *The formaldehyde study is unusual in that the "control" group was not in fact a zero-exposure group.*

3. *OEHHA does not intend to limit the use of the RELs to children alone. Health standards protective of children are necessary for any community exposure situation, where children may be (and usually are) present.*

Comments of the Manganese Interest Group on the Proposed Revisions to the Technical Support Document for Noncancer Reference Exposure Levels As Applied to Manganese (Prepared with the assistance of ENVIRON Int. and ENTRIX)

The entire 122 page comment including 2 tables, 74 footnotes, and 5 appendices is posted on the OEHHA webpage.

The appendices are:

Appendix 1: Summary of Data from North American Physiologically Based Pharmacokinetic (PBPK) Studies of Manganese

Appendix 2: Manganese PBPK Modeling

Appendix 3: Risk Assessment of Essential Metals

Appendix 4: Brief Overview of Epidemiological Investigations of Manganese

Appendix 5: A Critical Assessment of the Uncertainty Factors Applied in the Derivation of the Manganese REL

Introduction

The Manganese Interest Group (MIG) appreciates the opportunity to submit comments on the proposed revisions to the technical support document (TSD) for noncancer reference exposure levels (RELs) issued by the California Environmental Protection Agency's Office of Environmental Health Hazard Assessment (OEHHA) in November, 2007. MIG is an ad hoc coalition of trade associations and companies interested in the scientifically sound evaluation and regulation of manganese. MIG's members include steel producers, metalworkers, chemical manufacturers, and other like-minded stakeholders, some of which operate in California. Group members include: the American Iron and Steel Institute, the National Slag Association, the Steel Manufacturers Association, the Specialty Steel Industry of North America, DuPont, Afton Chemical Corporation, Evraz-Oregon Steel Mills, and U.S. Steel. MIG's members are impacted by the actions OEHHA has proposed with respect to manganese, both directly in the case of MIG's members that operate in California, and indirectly insofar as other states and regulatory authorities frequently rely upon actions taken by OEHHA to support their own actions pertaining to manganese or the methodology for setting reference exposure levels.[1]

MIG supports OEHHA's effort to refine the methodology for establishing RELs, including enhanced efforts to ensure the protection of infants and children. To that end, some elements of the proposed methodology are very promising for improving risk assessment, particularly the new methodology's clear recognition of the value of physiologically-based pharmacokinetic ("PBPK") models and benchmark-dose statistical analyses to refine and reduce uncertainties in the risk assessments conducted to determine RELs.

In MIG's view, however, the methodology recommended in OEHHA's technical support document ("TSD") was not appropriately applied in the case of manganese and the result was the derivation of manganese RELs that are overly conservative and that lack a basis in biological plausibility. Unique among the six chemicals addressed in OEHHA's proposal, manganese is both essential to human health (*including the health of infants and children*) and potentially

toxic. The essentiality of manganese adds an additional level of complexity for the REL development process, not present for any of the other five chemicals included in the OEHHA notice.

Through these comments, MIG seeks to provide OEHHA with important scientific information for manganese *not considered by OEHHA in its current analysis*. MIG also recommends ways to improve the application of quantitative risk assessment methodologies as applied to manganese. More specifically, MIG's comments explain that:

- OEHHA's has not adequately considered the substantial body of pharmacokinetic data for manganese that are currently being used to develop PBPK models for manganese. These data have a direct bearing on the biological plausibility of OEHHA's proposed RELs for manganese;

- OEHHA has not adequately considered the essentiality of manganese to human health, or explained why uptake of manganese from inhalation exposure must be limited to only a small fraction of a percent of the permissible amount from diet. In the case of adults, the proposed chronic manganese REL would limit manganese intake from inhalation to less than 1/18,000th of the maximum permissible intake from diet;

- OEHHA has omitted consideration of the substantial body of epidemiological studies concerning manganese that were completed before and after the 1992 Roels study on which the proposed manganese RELs are based. These omitted studies have a direct bearing on OEHHA's application of an uncertainty factor to account for less than chronic exposures;

- OEHHA has not considered the substantial body of existing benchmark-dose data concerning the 1992 Roels study. Benchmark statistical analyses of the 1992 Roels study and other similar studies have been available in the public literature for many years and should be considered;

- OEHHA has misconstrued some of the key studies upon which it has relied to support the proposed RELs for manganese. Most notably, there are no compelling scientific data to justify the use of two uncertainty factors of 10 for intraspecies toxicokinetics and toxicodynamics in OEHHA's derivation of the RELs for manganese; and

- OEHHA has not followed its proposed methodology in the derivation of the manganese RELs.

After reviewing these comments, MIG is hopeful that OEHHA will conclude that the substantial body of scientific information on manganese not considered in derivation of the draft RELs for manganese warrants their reconsideration. Further review of the available science will afford OEHHA an opportunity to address deficiencies in the initial application of the proposed methodology to manganese and to ensure OEHHA satisfies its statutory obligation to consider all available scientific data.

Comment 1:

I. MIG Commends and Supports OEHHA's Proposed Reliance Upon PBPK Models and Benchmark Dose Analyses in Risk Assessment.

OEHHA has proposed several methodological changes for developing acute, eight-hour and chronic RELs. From MIG's perspective, two of the proposed changes are particularly notable. First, where sufficient data are available, OEHHA now proposes that PBPK modeling be used to reduce interspecies and intraspecies uncertainty. Second, OEHHA also now proposes that where sufficient data are available, a benchmark dose approach is preferred over the traditional no observed adverse effect level (NOAEL) divided by uncertainty factors (UF) approach.

From a conceptual perspective, MIG supports both of these recommendations. In both cases, MIG prefers the quantitative approach that each method provides to address potential sources of uncertainty in contrast to the more arbitrary (and subjective) application of conventional uncertainty factors. The application of the PBPK models and a benchmark dose will provide for a more refined, scientifically robust, state-of-the-art risk assessment for manganese.

As OEHHA clearly recognizes, however, precisely how to apply PBPK models and benchmark analyses can and should vary, when appropriate, based on scientifically sound, "case-by-case" considerations. To that end, MIG agrees with OEHHA's goal of avoiding an overly "policy-oriented" method for deriving RELs. *OEHHA's methodology for deriving RELs should be sufficiently flexible to ensure sound scientific results in each case*, rather than formulaic in nature (i.e., requiring application of standardized "uncertainty factors" that may lead, in turn, to unnecessarily stringent health guidelines).

To this end, MIG recommends that OEHHA adopt a methodology for the derivation of RELs that provides OEHHA sufficient flexibility to consider relevant pharmacokinetic data for a particular substance (such as manganese) even if fully completed PBPK models based on that data are not yet available. As will be outlined in more detail in the ensuing sections, manganese presents an opportunity for OEHHA to exhibit the recommended flexibility and to avoid an overly policy-oriented method for derivation of RELs. Although only limited results are available from the manganese PBPK models currently under development, *the data on which those models will be based and validated are currently available and should be considered in the interim*.

Response:

OEHHA acknowledges and appreciates MIG's support of our proposed methodological changes including PBPK modeling and a preference for benchmark dose methodology. OEHHA's intention is to develop a methodology for deriving RELs that is sufficient to ensure sound scientific results in each case, while protecting the health of infants, children, and adults.

Comment 2:

II. OEHHA's Assessment of the Available Science for Manganese Is Incomplete.

Manganese is a ubiquitous element present in all natural environments. As an essential nutrient that is a natural component of many food groups, health experts have long recognized that animals (including humans) have elaborate homeostatic mechanisms that regulate how

ingested manganese is absorbed, distributed, metabolized, and eliminated by the body. The existence of these well-known homeostatic mechanisms has led regulatory authorities to conclude that the body is able to handle substantial variations in dietary manganese on a daily basis without adverse consequences.

What has not been known with similar precision until recently is whether these same homeostatic mechanisms regulate how the body handles *inhaled manganese*. This uncertainty prompted concerns that the long-term inhalation of even very low levels of manganese in ambient air might present a risk to public health because of the possibility that inhaled manganese might accumulate over time in various sensitive target tissues. Illustrating this concern, the U.S. EPA stated:

> Unlike ingested Mn, inhaled Mn is transported directly from the respiratory system to the vicinity of the brain before its first pass by the liver. Depending on the form of Mn inhaled, its conversion to other oxidation states (e.g., oxidation of Mn2+ to Mn3+ or reduction of Mn4+ to Mn3+), and its ability to enter the brain (through a protein transport mechanism or otherwise), *it is quite possible that a significant fraction of even small amounts of inhaled Mn would be able to reach target sites in the [central nervous system]*. Thus, the apparently greater toxicity of inhaled versus ingested Mn may reflect important pharmacokinetic differences of Mn that enters the body by different routes. *A more definitive understanding of these issues will require more empirical information.*

Since 1994 when the foregoing statement was made, a substantial body of information has been developed to provide the "more definitive understanding" sought by EPA concerning the pharmacokinetics of inhaled manganese. These studies, conducted over the past decade at the behest and supervision of regulatory authorities in the U.S. and Canada, provide a wealth of new data that is being used to develop PBPK models for inhaled manganese. As discussed in section II.A of these comments, both the pharmacokinetic data and the developing PBPK models show that homeostatic control mechanisms can effectively limit increases in target tissues at inhalation exposure concentrations that are an order of magnitude or more than the proposed RELs for manganese. OEHHA's current analysis omits consideration of this substantial body of pharmacokinetic studies, notwithstanding OEHHA's acknowledgement of their value and its corollary recommendation that PBPK models be used "wherever possible in order to address quantitatively the adequacy of acute and chronic RELs to protect the health of both children and adults."

OEHHA also presents inconsistent positions with respect to infants and children and manganese. On one hand, OEHHA asserts that "the still developing brain of newborn and infant children is more sensitive to the effects of manganese" and therefore in need of special additional protections. Separately, however, OEHHA clearly acknowledges that the recommended "adequate daily intake" of manganese in diet for newborns and infants (and children more generally) *increases substantially* as the typical diets of children change over time. OEHHA also clearly acknowledges that children can safely handle the substantial variations in daily dietary intake and absorption of manganese reflected in the recommended "upper limits" of dietary intake of manganese. OEHHA does not explain why uptake of manganese from inhalation exposure must be limited to only a small fraction of a percent of the permissible amount from

diet. In the case of adults, the proposed manganese REL would limit manganese intake from inhalation to less than 1/18,000th of the maximum permissible intake from diet. Now that pharmacokinetic studies have shown that target tissues are not particularly susceptible to manganese accumulation following low levels of manganese inhalation, OEHHA has the opportunity to reconsider the manganese RELs in light of this new information.

OEHHA has also omitted consideration of the substantial body of epidemiological studies concerning manganese that were completed before and after the study on which the proposed manganese RELs are based (i.e., Roels et al. 1992). These omitted studies have a direct bearing on OEHHA's application of an uncertainty factor to account for less than chronic exposures. Nor has OEHHA considered the substantial body of existing benchmark-dose data concerning the 1992 Roels study. Benchmark statistical analyses of the 1992 Roels study and other similar studies have been available in the public literature for many years. As in the case of PBPK models, OEHHA recommends that benchmark data be used "wherever possible," but OEHHA has omitted consideration of the available benchmark data for manganese without explanation. Review of the available benchmark data would reduce the level of uncertainty in the derivation of the manganese RELs.

Finally, OEHHA has misconstrued some of the key studies on which it relies to support the proposed RELs for manganese. More specifically, there are no compelling scientific data to justify the use of two uncertainty factors of 10 for intraspecies toxicokinetics and toxicodynamics in OEHHA's derivation of the RELs for manganese. The studies OEHHA relies upon as evidence of increased susceptibility in infants and children compared to adults (Wasserman et al. (2006), Ericson et al. (2006), Takser et al. (2003), Zhang et al. (1995) and Collip et al. (1983)) provide no such evidence. None of the studies cited by OEHHA evaluated manganese toxicokinetics, such as gastrointestinal absorption, homeostasis of blood manganese levels, or issues related to the integrity of the blood brain barrier in infants or children. Moreover, these studies could not be used to assert that children are more susceptible to neurotoxicity than adults, a toxicodynamic difference, because none of the studies evaluated adults or compared their findings to those in adults with similar exposure or similar endpoints.

Below we outline how the consideration of additional important scientific data on manganese would provide for the development of more refined and scientifically robust RELs by OEHHA.

Response:

Inhalation of manganese represents a route of exposure that is qualitatively different from the oral route. Manganese absorbed from the digestive tract is subject to first-pass removal by the liver before it can reach other tissues. While this enterohepatic circuit functions very effectively to regulate dietary manganese, manganese entering the blood from the respiratory tract avoids this first pass removal by the liver and goes directly to the tissues, including the brain. In addition, numerous studies have shown that inhaled manganese can reach the brain more directly via transport from the nose along olfactory nerves to the olfactory bulb, with subsequent translocation to other brain structures. This route not only avoids hepatic first pass removal, it also avoids the blood brain barrier.

Other chemicals which are toxic by inhalation and relatively innocuous by the oral route are respirable crystalline silica, beryllium, hexavalent chromium, and nickel.

In regard to the "substantial body of epidemiological studies concerning manganese that were completed before and after the study on which the proposed manganese RELs are based (i.e., Roels et al. 1992)," OEHHA staff did not believe that they were on the same level with the Roels et al. (1992) study. For example, Roels et al. (1987) reported that a *TWA exposure to airborne Mn (total) dust of about 1 mg/m^3 for less than 20 years may present preclinical signs of intoxication. The authors did not find dose-response relationships between Mn in the urine or the duration of Mn exposure and the prevalence of abnormal CNS or biological findings. However we have included the studies in the revised REL summary for completeness.*

In regard to the benchmark analysis, only recently were the raw data needed to conduct the analysis made available to OEHHA. OEHHA has calculated a BMCL from the raw data using BMDS, and now uses this point of departure to calculate RELs.

Comment 3:

A. Comprehensive Data on the Pharmacokinetics of Inhaled Manganese Provide Quantitative Results That Reveal the Relationship Between Inhaled Manganese and Tissue Concentrations. MIG Encourages OEHHA to Take These Data Fully Into Account for the Risk Assessment of Manganese.

Regulatory authorities and other health experts have identified a number of factors that potentially impact whether inhaled manganese presents a risk to public health. The principal sources of uncertainty (in addition to the overarching uncertainty concerning the existence of homeostatic control of manganese entering the body via inhalation) include:

• The existence of *potentially sensitive subgroups* within the population (e.g., the very old or the very young);

• The possibility that *different forms of manganese* might impact uptake and distribution of manganese within the body;

• The possibility that the brain is not *the most sensitive organ* for potential manganese toxicity;

• The possibility that the *duration of exposure* might impact manganese homeostasis within the body; and

• The potential that *dietary and inhaled manganese may interact*, altering how manganese accumulates in body tissues.

To address these sources of uncertainty, regulatory authorities in North America have commissioned a series of pharmacokinetic studies over the past decade that have evaluated how each potential source of uncertainty impacts the accumulation of manganese in target tissues. Independent researchers at the Chemical Industry Institute for Toxicology (now the Hamner Institutes for Health Sciences) conducted a manganese health research program mandated by the U.S. EPA under the U.S. Clean Air Act. This

program consisted of manganese inhalation studies in rodents and non-human primates. Also, independent researchers at the University of Montreal conducted a second set of studies that was sponsored jointly by Health Canada and Environment Canada.

Comprised of a series of distinct, short-term and sub-chronic experiments, these North American studies provide a wealth of information directly addressing the potential "pharmacokinetic differences" essential to assessing the risks of inhaled manganese as described below.

- Forms of manganese: The North American studies evaluated five different forms of manganese representing both ends of the solubility spectrum for manganese compounds. The five forms of manganese were the relatively insoluble Mn_3O_4, the somewhat more soluble $MnPO_4$, the relatively soluble $MnSO_4$, a mixture of $MnPO_4$ and $MnSO_4$, and pure metallic manganese.

- Animal ages and gender: The programs included both rats and monkeys. The studies evaluated both male and female animals in sixteen different age groups, ranging from fetal animals to senescent (old) animals.

- Exposure levels: The studies evaluated how tissue concentrations changed over nearly two dozen different exposure concentrations, ranging from as little as 4 micrograms manganese per cubic meter of air ("μg Mn/m^3") to 3,750 μg Mn/m^3. These exposure concentrations correspond to ambient environmental levels as low as 0.7 μg Mn/m^3 and as high as 670 μg Mn/m^3.

- Dietary manganese: The studies evaluated how tissue concentrations changed over four dietary manganese levels (2 parts per million ("ppm"), 10 ppm, 100 ppm, and 125 ppm) administered with different inhalation exposure concentrations.

- Exposure durations: The studies included a range of exposure durations, ranging from short-term, 14-day exposures to sub-chronic 90-day exposures. The studies also evaluated tissue concentrations and manganese excretion rates for up to 90-days post-exposure.

- Manganese elimination: The studies involved injection of radio-labeled manganese to evaluate manganese elimination kinetics following inhalation exposure.

Collectively, the experiments that comprised the North American pharmacokinetic studies generated thousands of data points for analysis. Because most of the data are measurements of manganese tissue concentrations, the resulting database can be used to assess whether the listed variables impact homeostatic control of inhaled manganese in the body, and if so, to what degree. PBPK models for manganese will quantify these interrelationships mathematically.

The PBPK models for inhaled manganese are currently being developed and refined by scientists at the Hamner Institutes for Health Sciences in Research Triangle Park, North Carolina. Appendix 2 provides additional information concerning the scientific value of the manganese PBPK models and their current status. Although the complete suite of PBPK models for manganese are not yet available (they will be completed in 2008), *the studies that generated*

the data being used to develop and validate the models are available in the peer-reviewed literature. Pending completion of the PBPK models, a review of the studies on which they are based illustrates in practical terms the potential power and importance of the PBPK models for refining OEHHA's risk assessment for manganese.

Response:

OEHHA will review the PBPK models when made available in a final peer-reviewed document. To develop our document we had to rely on the data available at the time of our review. We note that five of the Dorman et al. papers on manganese were cited in our REL summary.

Comment 4:

1. The Results of the Pharmacokinetic Manganese Studies

A complete listing of the pharmacokinetic manganese studies appears in the bibliography contained in Appendix 1, which also provides a summary of some the key data derived from the studies. All of the pharmacokinetic manganese studies have been peer-reviewed, in some cases more than once. The major findings from the studies are presented below.

• **The respiratory tract is an important portal of entry for manganese.**

The results of the manganese pharmacokinetic studies confirm the observation that "as a route of Mn exposure, the respiratory tract is the most important portal of entry." Provided the inhalation concentration is sufficiently elevated, the study results confirm that inhaled manganese quickly accumulates in tissues separate from the lung, including sensitive portions of the brain of both rats and primates. This outcome is consistent with the observation that "[a]fter absorption via the respiratory tract, Mn is transported through the blood stream directly to the brain, bypassing the liver and the opportunity for first-pass hepatic clearance." Appendix 1 clearly shows nearly universal increases in manganese tissue concentrations in both rats and primates (regardless of age or gender) whenever the inhalation exposure concentration is sufficiently elevated. As explained more fully below, however, the study results summarized in Appendix 1 also show that (1) manganese is a natural and highly variable component of body tissues with and without elevated inhalation exposure, and (2) manganese absorbed from the lung at lower levels of inhalation exposure does <u>not</u> accumulate in body tissues, including the brain, despite "bypassing . . . first pass hepatic clearance." This latter conclusion applies regardless of age or gender.

• **Manganese is a natural and highly variable component of body tissues.**

Manganese is a natural component of brain and other tissues in both the rat and the primate, regardless of age or gender. Moreover, the concentration of manganese varies from one tissue to the next and from one animal to the next for any specific tissue, even in the absence of exposure to inhaled manganese. This variability suggests that the body naturally accommodates a range of manganese tissue concentrations, whether due to genetic, dietary, or other factors.

- **Homeostatic control of inhaled manganese limits the accumulation of manganese in bodily tissues, including the brain.**

Animals exposed to manganese through inhalation develop dose-dependent biliary and pancreatic excretion of manganese that serves to regulate the amount of manganese retained by the body and to limit increases in the manganese content of brain, liver, or other tissues. As the inhalation exposure level increases, the amount of biliary and pancreatic excretion similarly increases. This dynamic applies in both primates and rats. Increased biliary and pancreatic excretion of manganese occurs rapidly once exposure to inhaled manganese commences and also quickly returns to normal levels following cessation of exposure. As a result, inhaled manganese that enters the brain or other tissues is not permanently sequestered. Elimination occurs relatively quickly, with a half-life less than 45 days (in the case of primate globus pallidal tissue).

Homeostatic control of oral and/or inhaled manganese is not altered by diets either very low or very high in manganese content, nor by the form of inhaled manganese. Diets ranging from 2 ppm to 125 ppm did not materially impact accumulation of manganese in tissue with inhalation exposures to different forms of manganese.

In primates, the largest relative changes in manganese tissue concentration following inhalation exposure occur in olfactory tissues, the pituitary gland, and the striatal region of the brain (globus pallidus, caudate and putamen). These results confirm the view that inhaled manganese is preferentially taken up by the mid-brain regions that influence motor control. In rats, the largest relative changes in manganese tissue concentration occur in the olfactory bulb, the lung, and the striatal region of the brain (globus pallidus, caudate and putamen). In both primates and rats, reproductive organs accumulate manganese only at higher concentrations than those that lead to accumulation in some brain tissues (e.g., globus pallidus, caudate and putamen) suggesting, consistent with existing data, that potential neurological effects from inhaled manganese are more sensitive indicators than potential reproductive effects.

Finally, for every target tissue analyzed, the dose-response data show that a threshold inhalation exposure dose exists *at or below which no measurable change in manganese tissue concentration occurs*. This conclusion applies even in the case of potentially sensitive subpopulations, including the very old and the very young. The fact that manganese tissue concentrations in the brain and other systemic organs do not change at lower inhalation exposure levels (i.e., at or below approximately 0.5 μg Mn/m^3) suggests that the body can naturally accommodate lower levels of manganese in air without impact notwithstanding that absorbed manganese from the lung, unlike ingested manganese, bypasses first-pass hepatic clearance.

- **Subpopulations considered potentially susceptible to increased manganese accumulation develop quantitatively similar end-of-exposure brain and tissue manganese concentrations when compared with young adult males.**

Gender and age differences did not lead to significant variations in manganese accumulation and did not affect delivery of manganese to the striatum, a known target site for neurotoxicity in humans.

Fetal brain manganese concentrations were not affected by maternal exposure to high doses of inhaled manganese. The rat placenta and fetal liver effectively sequesters manganese, limiting manganese delivery to the fetal brain.

In neonatal animals, tissue Mn concentrations depend upon the age of the developing animal and route of exposure (e.g., inhalation, oral via milk, or a combination of the two). As

with other age and gender groups, the data demonstrate that (i) there is a threshold inhalation exposure dose for manganese at or below which no material change in target tissues of interest occurs, and (ii) neonatal animals, regardless of gender, are not susceptible to enhanced accumulation of manganese in target tissues when compared to mature animals.

- **Rats and primates exhibit qualitatively similar pharmacokinetic control of inhaled manganese suggesting that rat data may be used to model the pharmacokinetics of inhaled manganese in humans.**

It has long been thought that rodents do not exhibit the same toxicological sensitivity as primates to the toxicological effects of accumulation of manganese in brain regions that influence movement. The manganese pharmacokinetic studies show, however, that rats and primates *exhibit qualitatively similar pharmacokinetic control of inhaled manganese independent of any toxicological differences that may exist between the species*. Both rats and primates eliminate inhaled manganese from the body by means of increased bile and pancreatic secretion of manganese. These mechanisms commence quickly in both species once exposure begins. Both rats and primates also show accumulation in brain and other bodily tissues with sufficiently high inhalation exposure concentrations, although at somewhat different relative rates. In both cases, moreover, brain tissue shows higher relative manganese accumulation than most other body tissues. Both rats and primates also exhibit a similar capability of eliminating increases in manganese tissue concentrations once exposure ends. Thus, even if an accumulation of manganese in rat tissue does not lead to a discernable toxicological effect similar to that seen in primates, the processes controlling how manganese gets from the lung to more distant organs is qualitatively similar for both the rat and the primate. For this reason, the pharmacokinetic data generated in rats can reasonably be used to model the pharmacokinetics of inhaled manganese in primates (without regard for toxicological impacts), and, by extension, to humans.

Response:

As stated above, OEHHA will review the PBPK models when made available in a final peer-reviewed document. However, we will continue to develop the Mn RELs with information currently available. Further, there is evidence in the peer-reviewed literature that homeostatic mechanisms are lacking in the newborn and that brain concentrations are elevated from in utero and postnatal exposures. This may lead to a risk of developmental neurotoxicity, which has been reported in association with manganese in drinking wate , elevated levels in cord blood, and teeth in children. These studies are discussed in our REL summary.

Comment 5:

2. In Addition to Supporting Development of PBPK Models for Manganese, Application of Pharmacokinetic Data to a Risk Assessment for Manganese Will Ensure that OEHHA's Proposed Manganese RELs are Biologically Plausible.

For the most part, the North American studies on manganese summarized in the preceding section did not focus on assessing whether a change in manganese tissue concentration was associated with any particular adverse impact. Instead, the studies addressed a more basic question – namely, how do tissue concentrations change, if at all, as a function of different levels

of exposure to different species of manganese in air? The answer to this more basic question has important ramifications for a manganese risk assessment and, ultimately, regulatory guidelines.

The data generated in the recent North American studies (and the PBPK models for manganese that are under development) provide an empirical basis upon which to evaluate the biological plausibility of applying multiple uncertainty factors to derive inhalation RELs for manganese. "Biological plausibility" is one of several key concepts that govern the assessment of scientific data in the REL development process. As explained by OEHHA in its new methodology, "[a] 'weight of evidence' approach is generally used to describe the body of evidence on whether or not exposure to a chemical causes a particular effect" where "the number and quality of toxicology and epidemiological studies, *as well as data on biological plausibility*, are considered in making scientific judgment." Stated another way, biological plausibility requires that "[a] causal interpretation [not] conflict with what is known about the biology of the disease" at issue.

The proposed manganese RELs are based on OEHHA's assessment of an occupational epidemiological study that evaluated whether and how inhaled manganese impacted workers at an alkaline battery production plant (Roels et al. 2002). Based on the findings reported in this study, OEHHA concluded that exposure to 150 μg Mn/m³ resulted in small, sub-clinical reductions in the fine motor control, memory, and visual acuity of the workers. Because this level of exposure occurred during an 8-hour work day, OEHHA equated it to a continuous exposure to 54 μg Mn/m³, or what is known as a "lowest observed adverse effect level" (or LOAEL). OEHHA then applied four uncertainty factors ranging from 3.16 to 10 to generate a "chronic" manganese REL of 0.03 μg Mn/m³:

(1) A factor of six to reduce the LOAEL to a presumptive NOAEL (from 54 μg Mn/m³ to 9.0 μg Mn/m³);

(2) A factor of 3.16 to account for less than chronic exposure in the battery plant study (from 9.0 μg Mn/m³ to 3.0 μg Mn/m³); and

(3) Two factors of 10 to account for the potential sensitivity of infants and children: one factor of 10 to account for potential differences in toxicokinetics (i.e., greater lung deposition in children) and a second factor of 10 to account for potential differences in toxicodynamics (i.e., a greater susceptibility of children to neurotoxicity) (from 3.0 μg Mn/m³ to 0.3 μg Mn/m³ and from 0.3 μg Mn/m³ to 0.03 μg Mn/m³, respectively).

The biological plausibility of OEHHA's LOAEL of 54 μg Mn/m³ is reasonably clear because at that level of exposure the body's uptake of manganese on a daily basis would likely increase by about a factor of three or more over and above the typical uptake of manganese from the diet. The dose response data from the recent manganese pharmacokinetic studies shows, moreover, that the manganese content of key brain tissues, such as the globus pallidus, *increases by a factor of more than 2.5* in the primate at the LOAEL exposure concentration derived from the 1992 Roels study.

Increasingly less clear, however, is the biological plausibility of the consecutive application of the additional uncertainty factors. The application of each uncertainty factor is biologically plausible only if the reduction in the manganese exposure dose that such factors provide for is associated with a parallel reduction in the concentration of manganese in target tissues of interest. The dose response data from the recent manganese pharmacokinetic studies show, however, that this implicit assumption is not valid in the case of manganese *below a certain threshold of exposure*.

As noted, for every target tissue analyzed, the dose-response data show that a threshold inhalation exposure level exists *at or below which no measurable change in manganese tissue concentration occurs*. Tables 1 through 8 in Appendix 1 show no measurable change in *any* tissue concentrations of interest occurs at or below an exposure concentration of approximately 0.5 μg Mn/m³, regardless of age or gender. In fact, for many tissues, the exposure level at which no change in manganese tissue concentration was measured or projected is substantially higher.

A central principle of quantitative risk assessment is that *no toxicologically material impact can occur from a compound without a corresponding change in tissue concentrations of the compound*, and this principle applies to manganese. Only two orders of magnitude (i.e., a factor of 100) separate the "effect" level on which the manganese REL is based (i.e., the LOAEL of 54 μg Mn/m³) and a level of exposure at which no measurable changes in manganese tissue concentration have been found to occur in either rats or primates in <u>any</u> tissue (i.e., approximately 0.5 μg Mn/m³). The existence of a threshold inhalation exposure level for manganese at or below which manganese tissue concentrations do not change in rats and primates has a direct bearing on the "biological plausibility" of OEHHA's 2000-fold uncertainty factor. It suggests that the maximum biologically plausible uncertainty factor that should be applied to OEHHA's LOAEL is something on the order of 100, not 2,000. This means, in turn, that OEHHA's proposed "chronic" manganese REL may be more than an order of magnitude lower than necessary.

Finally, even a manganese REL developed with consideration of existing pharmacokinetic data for manganese would likely be highly conservative. Target tissues in the body likely can accommodate modest manganese increases *without any adverse impact*. The primate study shows, for example, that exposure to 9.0 μg Mn/m³ results in a projected 30 to 50 percent increase in the manganese concentration of the globus pallidus, putamen and caudate regions of the primate brain. Because 9.0 μg Mn/m³ is deemed at present to be a *de facto* NOAEL in otherwise healthy adult humans, humans (like the primate) can presumably accommodate modest increases in brain manganese concentrations with no ill effect.

In short, the results of studies investigating the pharmacokinetics of inhaled manganese show that homeostatic mechanisms regulate the presence of manganese in the body from inhalation just as homeostatic mechanisms also apply to control ingested manganese. Confirmation that homeostatic mechanisms regulate how inhaled manganese is handled in the body directly addresses the concern expressed by regulatory authorities in the past that inhalation of small concentrations of manganese might lead to the accumulation of manganese in target tissues over time. *Manganese accumulation in target tissues (and the potential for toxicity that such accumulation might entail) does not occur when the level of manganese in air is low (i.e., at or below approximately 0.5 μg Mn/m³), even for those tissues that are most sensitive*. Accumulation in target tissues begins to occur only when animals (regardless of their age or gender) are exposed to levels of manganese in air far higher than those currently measured in large urban areas in California (and far higher than OEHHA's proposed manganese RELs). These findings suggest that the RELs for inhaled manganese proposed by OEHHA have been set at levels far below the actual levels at which biologically plausible accumulation (and the potential toxicity such accumulation *might* entail) can or does occur.

Response:

The comment is primarily concerned that the cumulative uncertainty factor in the draft REL is too large. One of the issues raised in this comment is that of homeostatic control of manganese levels. The enterohepatic homeostatic control of manganese absorbed in the diet appears to be well understood, but there is less certainty about the homeostatic mechanisms at work in the CNS, especially in human neonates. Now that OEHHA obtained the data for individuals in the Roels et al. (1992) study, we have conducted our own BMD analysis which eliminates the LOAEL UF, and lowers the cumulative UF to 300. However, uncertainties remain regarding neonatal Mn homeostasis and the significance of the accumulation of Mn in the brains of primates in the regions of the globus pallidus, putamen and caudate at the putative NOAEL of 9 µg/m^3 mentioned above Furthermore, the biological plausibility for developmental neurotoxicity is well-established since manganese exposure in adults is neurotoxic. The developmental stages of the CNS generally confer high sensitivity to neurotoxicants relative to an adult animal.

Comment 6:

B. The Implications of the Essentiality of Manganese to Human Health, Including the Health of Infants and Children, Have Not Been Properly Considered by OEHHA.

The conduct of risk assessments for an element such as manganese presents challenges because of the need to consider the balance between essentiality (i.e., the fact that the element is necessary for good health) and toxicity. For each essential trace element, there are two ranges of intake associated with adverse health effects: intakes that may result in nutritional deficits because they are too low and intakes that may result in toxicity because they are too high. Between these two ranges, there is a range of safe and adequate intakes that is compatible with good health; however, the challenge is to define that range quantitatively.

OEHHA proposes that the RELs for inhaled manganese must be reduced to account for two principal concerns pertaining to infants and children: (1) "the expectation that *the developing brain is more sensitive to manganese* and that any injuries to the nervous system during development are anticipated to have lasting effects;" and (2) "*the 3-4 fold greater deposition of inhaled particulates* in the 1-10 µm size range in the lungs of neonates relative to adults exposed to similar particulate levels in ambient air" coupled with concern that "neonates accumulate higher levels of manganese in the brain more quickly than do adults with similar exposures." Regarding both concerns, OEHHA has misconstrued the available science.

1. Manganese is Essential to the Maintenance of Human Health, Including the Health of Infants and Children. MIG Urges OEHHA to Fully Consider the Implications of Manganese Essentiality.

OEHHA acknowledges that manganese is essential for human health at all life stages, but fails to account for essentiality when it separately states that "the developing brain is more sensitive to manganese." In Appendix D of OEHHA's new methodology, Table 6.5.1 lists the "adequate daily intake" (ADI) of manganese by diet for males and females from infancy to old age. Rather than confirming that "the developing brain is more sensitive to manganese," Table 6.5.1 actually shows that manganese is essential for normal and healthy development of infants and children.

The table below restates what OEHHA has shown in Table 6.5.1, but adds a new column showing the degree to which the adequate daily intake of manganese *increases with each life stage*.

Relative Changes in the Adequate Daily Intake (ADI) for Manganese by Life Stage

Age Group	ADI (mg/day)	% Change from Prior Age Group
Infants, 0-6 months	0.003	NA
Infants, 7-12 months	0.6	+20,000%
Children, 1-3 years	1.2	+200%
Children, 4-8 years	1.5	+25%
Boys, 9-13 years	1.9	+27%
Boys, 14-18 years	2.2	+16%
Men, 19 to >70 years	2.3	+5%
Girls, 9-13 years	1.6	+7%
Girls, 14-18 years	1.6	NC
Women, 19 to >70 years	1.8	+11%
Pregnant women, 14-18 years	2.0	+25%
Pregnant women, 19-50 years	2.0	NC
Lactating women, 14-18 years	2.6	+63%
Lactating women, 19-50 years	2.6	NC

The table clearly shows that developing humans consume more manganese as they age. The table also clearly shows that the relative increase in ADIs for manganese is much higher from one stage of early development to the next compared to later stages of development.

The increasing consumption of manganese in the diet necessarily entails *increased* absorption into the body because, as OEHHA recognizes, infants and children "absorb greater amounts of manganese in the gastrointestinal tract." The increased systemic manganese from ingestion in infants and children is highly suggestive that manganese is essential to normal development because, as OEHHA also clearly recognizes, "[m]anganese is an essential nutrient involved in the formation of bone, and in amino acid, cholesterol, and carbohydrate metabolism." But even if not strictly necessary for healthy development, the increased systemic manganese that results from normal dietary consumption as infants and children age is *not* consistent with OEHHA's blanket statement that "the developing brain is more sensitive to manganese." If true, the ADIs for infants and children would be cause for concern, but they are not. The available scientific data show that no adverse effects have been found in a wide range of populations, including infants and children, consuming diets with markedly different manganese content over extended periods of time.

Finally, the manganese ADI also increases substantially for pregnant and lactating women. This further undercuts OEHHA's assertion that "the developing brain is more sensitive to manganese." The fact that pregnant or lactating women need more manganese is additional compelling evidence that manganese is essential to proper development of infants and young children.

Response:

The essentiality of manganese in the diet is not disputed, nor is it disputed that dietary requirements change with age. In fact, our REL summary has a discussion of this issue with tables of daily requirements. Thus it is not correct to implicate that OEHHA did nit consider the essentiality of manganese as a micronutrient. The concern is whether inhaled manganese, which bypasses the body's normal regulatory mechanisms, can accumulate in the brain at levels that result in toxicity. The studies of workers with adverse neurobehavioral changes following occupational inhalation exposure to manganese suggest that this is the case.

While it is true that a wide range of dietary manganese levels appears compatible with normal healthy functioning, there are studies reporting associations between high manganese consumption via drinking water and decrements in intellectual functioning in children (Wasserman et al., 2006), between high cord blood manganese and developmental neurotoxicity (Takser et al., 2003), and between high manganese intake from parenteral feeding and brain and liver dysfunction (Komaki et al., 1999; Fell et al., 1996). These and other studies are described in our REL summary.

Comment 7:

2. Neonates Do Not Accumulate Higher Levels of Manganese in the Brain More Quickly Than Adults Do With Similar Exposures.

OEHHA asserts that neonates accumulate higher levels of manganese in the brain more quickly than adults with similar exposures. To support this assertion, OEHHA relies upon a study which actually shows *that just the opposite is true*. The neonatal exposure study conducted by Dr. Dorman and associates demonstrated that manganese tissue concentrations in the developing rat resulting from exposure to manganese in air are subject to strict homeostatic control. This was demonstrated in four distinct but interrelated ways. First, brain manganese concentrations actually fell by 17 percent from post-natal day (PND) 1 to PND 14 for neonatal rats exposed to the low inhalation dose of the highly soluble $MnSO_4$ (i.e., 50 μg Mn/m^3), while the neonatal rats exposed to higher levels in air showed dose-dependent levels of accumulation (which may be attributable to the ingestion of milk containing far higher levels of manganese, rather than the inhalation exposure itself).

Second, no evidence of enhanced accumulation of manganese in any discrete brain tissues occurred by the end of PND19 compared to young adult rats. In fact, as shown in the table below, neonatal rats exposed to the lowest inhalation exposure concentration for manganese had *lower* brain manganese concentrations than their adult counterparts, despite having been exposed to more than double the amount of manganese on a cumulative basis.

Comparison of Brain Manganese Tissue Concentrations (μg Mn/g) for Young Adult and Neonatal Rats (PND19) Exposed to Low Manganese Inhalation Exposures

Age	Olfactory Bulb	Striatum	Cerebellum	Exposure Period	Mn Concentration and Cummulative Exposure[48]
Young Adult	1.06	0.76	0.58	14-day	30 µg Mn/m³ 2,520 µg Mn
PND19	0.54	0.62	0.51	19-day	50 µg Mn/m³ 5,700 µg Mn

Third, the neonatal rats showed clear evidence of inhalation dose-dependent manganese tissue concentrations in both the liver and pancreas, suggesting that the liver and pancreas store manganese in the developing rat, either for use in developing tissue or excretion as the biliary system matures. Finally, elevated brain manganese levels in the neonatal animals exposed to inhaled manganese at higher concentrations returned to the levels of the non-exposed animals within 26-days after the cessation of exposure.[50] None of these findings are consistent with OEHHA's assertion that neonates accumulate manganese in brain tissue more readily than adults.

Response:

This assertion is at odds with a study by Dorman et al. (2000) in which neonatal and adult rats were orally exposed to comparable levels of manganese dichloride for the same period of time. In this study, neonates did indeed accumulate higher levels of manganese than did the adults in five of six brain areas: cerebellum, hindbrain, hippocampus, hypothalamus, and residual, but not the striatum. Compared to controls, there were statistically significant increases in neonates in all six areas at the high dose (50 mg/kg), and in four of the areas at the low dose (25 mg/kg). Also compared to controls, the neonatal rats with high manganese exposure showed statistically significant increases in acoustic startle reflex; an effect not observed in adults.

In any event, the important issue is not whether manganese accumulates more quickly in neonates than in adults but whether young animals experience more severe effects than adults with comparable exposure, or comparable effects with shorter or lower exposure. This was suggested in studies that found evidence of neuronal degeneration in adult rats after 120 days of exposure, but after only 30 days in young rats with comparable exposure levels (Chandra and Shukla, 1978; Chandra and Srivastava, 1970).

Exposure of rats to airborne manganese (MnSO4) in utero and postnatally increased oxidative stress as shown by significantly lowered GSH:GSSG ratios in the striatum, hippocampus, and olfactory bulb on postnatal day 19 (Erikson et al., 2006). A related marker, glutamine synthetase, was significantly lowered in the cerebellum, while glutamine synthetase mRNA and metallothionein mRNA levels were lowered in the striatum.

There are also studies indicating that, at least in two model in vitro systems, murine neural stem cells (NSC, line C17.2) and primary cultures of rat embryonic NSCs (cNSCs) were more vulnerable to Mn (50, 100, 250 µM as $MnCl_2$) toxicity than were hippocampal neuronal cells (line HT22) or astrocytoma cells (line D384) (Tamm et al., 2008). The stem cells showed

elevated production of reactive oxygen species compared to controls and underwent mitochondrial-mediated apoptotic death. In the more differentiated cell types, a significant toxic effect was seen HT22 cells only at higher doses (500 – 1,000 µM), while the D384 cells were not affected at these doses. The data suggest that undifferentiated cells, such as are found in developing nervous systems, may be more susceptible to Mn toxicity. That the developing nervous system is more vulnerable to toxic insult than that of the adult has been shown for a wide range of substances (Rice and Barone, 2000). OEHHA discusses several studies that provide evidence for developmental neurotoxicity in humans exposed to manganese in the drinking water, or with elevated hair, tooth or cord blood manganese.

Comment 8:

3. Limiting the Intake of Manganese from Air to a Mere Fraction of the Tolerable Daily Intake of Manganese from Diet Has Not Been Justified.

In addition to reporting the ADI for manganese in Table 6.5.1 of Appendix D, OEHHA also reports the tolerable "upper limit" (UL) of intake of manganese for humans at all life stages. Like OEHHA's proposed manganese RELs, the upper limits for dietary intake of manganese have been set to protect against potential neurological effects.

The table below replicates the information from OEHHA's Table 6.5.1, including the ULs where established, but also adds conservative projections of the change in uptake from the ADI to UL guidelines compared to projected uptake from manganese in air at the level of the proposed chronic manganese REL. The projected uptake from diet assumes the following absorption percentages of dietary intake of manganese: 100 percent in infants (0 to 6 months of age), 10 percent in children 7 months to 4 years of age, and 5 percent for all other age groups. The projected uptake from air conservatively assumes that all inhaled manganese is absorbed by the body based on the relative "applied doses" OEHHA reported for different age groups in Figure 8.1 of Appendix D. To determine the amount of air breathed per day for each of the age groups depicted in Figure 8.1, the total applied dose was divided by 0.215 mg Mn/m³. By necessity, the relative absorption figures from inhalation are approximate because OEHHA did not report the specific numbers or assumptions used to develop Figure 8.1 of Appendix D.

Comparison of Air and Dietary Uptake of Manganese Using Conservative Assumptions

Age Group	ADI (µg/day)	UL (µg/day)	Uptake Range from Diet (µg Mn)	Uptake from Air (µg Mn)	% of ADI	% of UL
Infants, 0-6 months	3	ND	3.0	0.13	4.3%	NA
Infants, 7-12 months	600	ND	60	0.13	0.2%	NA
Children, 1-3 years	1200	2000	120-200	0.21	0.2%	0.1%
Children, 4-8 years	1500	3000	150-300 (4 yrs) 75-150 (>4 yrs)	0.24 (3-5 yrs) 0.28 (6-8 yrs)	0.2% 0.4%	0.1% 0.2%
Boys, 9-13 yrs	1900	6000	95-300	0.42 (9-11 yrs) 0.45 (12-13	0.4% 0.5%	0.1% 0.2%

				yrs)		
Boys, 14-18 yrs	2200	9000	110-450	0.45 (14-15 yrs) 0.53 (15-18 yrs)	0.4% 0.5%	0.1% 0.1%
Men, 19 to >70 yrs	2300	11,000	115-550	0.45	0.4%	0.1%
Girls, 9-13 yrs	1600	6000	80-300	0.42 (9-11 yrs) 0.45 (12-13 yrs)	0.5% 0.6%	0.1% 0.2%
Girls, 14-18 yrs	1600	9000	80-450	0.45 (14-15 yrs) 0.53 (15-18 yrs)	0.6% 0.7%	0.1% 0.1%
Women, 19 to >70 yrs	1800	11,000	90-550	0.45	0.5%	0.1%
Pregnant women, 14-18 yrs	2000	9000	100-450	0.45 (14-15 yrs) 0.53 (15-18 yrs)	0.5% 0.5%	0.1% 0.1%
Pregnant women, 19-50 yrs	2000	11,000	100-550	0.45	0.5%	0.1%
Lactating women, 14-18 yrs	2600	9000	130-450	0.45 (14-15 yrs) 0.53 (15-18 yrs)	0.3% 0.4%	0.1% 0.1%
Lactating women, 19-50 yrs	2600	11,000	130-550	0.45	0.3%	0.1%

In all cases, the projected uptake from air at the level of the proposed chronic manganese REL is only an extremely small fraction of the ADIs for manganese and an even smaller fraction of the ULs for manganese in diet. By contrast, Figure 8.1 in Appendix D of OEHHA's proposal shows a very different result. Figure 8.1 shows that the dose from manganese in air *doubles (and, in some cases, triples)* when all age groups are exposed to "the levels reported in the Roels et al. (1992) occupational study (0.215 mg/m^3)."

OEHHA has not explained why minute amounts of manganese absorbed into the body from air should be deemed hundreds to thousands of times more "toxic" than ingested manganese. Because manganese can cause neurological effects regardless of the route of exposure at certain doses, OEHHA must have a scientifically sound rationale for setting manganese inhalation RELs at such a small fraction of existing dietary standards for manganese. In the past, one potential rationale was the possible existence of "important pharmacokinetic differences of Mn that enters the body by different routes." That issue has now been addressed with the substantial body of pharmacokinetic studies for manganese described in the proceeding section of this document. Absent a different rationale (which has not yet been identified), OEHHA has not established, as it must, the biological justification of such low RELs for inhaled manganese.

Response:

OEHHA derives a rather different picture from the data for adequate daily intakes (ADI) and tolerable upper intake levels (UL) presented in Table 6.5.1 of the REL document. The table below presents the data taken from Table 6.5.1 and inhalation rates per kilogram body weight per day from Arcus and Blaisdell (2007) and our Technical Support Document for Exposure Assessment and Stochastic Analysis (OEHHA, 2000). As in the comment's example, we assume that uptake from the lungs is 100% of the inhaled manganese (0.215 mg Mn/m^3), absorption from dietary intake is 100% for 0-1 yrs, 10% for 2-3 yrs, and 5% for all other ages. The inhaled Mn becomes the age- specific breathing rate times the air concentration. For comparison, the levels of Mn expected from an adequate diet and from intake at the upper limit are presented. Under these exposure conditions, inhaled Mn is higher than the adequate dietary intake for children 2-8 years old (% of ADI). As shown in the far right column (% of UL), the Mn inhaled by children 2-11 years of age on a per weight basis is a much higher percentage of the upper limit than it is for adults. In other words, for comparable air exposures, children are more at risk for exceeding safe levels from diet alone than are adults. One of the large uncertainties is how well infants and small children regulate Mn levels when exposed by both routes. Studies by Dorman et al. (2001) suggest that in adult rats, manganese inhalation increased Mn clearance, but increased dietary intake did not affect the accumulation of Mn in the brain. This result strengthens our assertion that comparisons with the oral route are not particularly meaningful.

Comparison of Manganese Uptake by Inhalation and Diet.

Age (y)	Air inhaled m^3/kg-d	Mn inhaled mg/kg-d	Adequate (ADI) mg/d	UL mg/d	Uptake from diet (%)	From diet mg/d	UL mg/d	% of ADI	% of UL
0-1	0.705	0.152	0.6	ND	100	0.6	ND	25	ND
2-3	0.656	0.141	1.2	2	10	0.12	0.2	118	71
3-5	0.613	0.132	1.5	3	5	0.075	0.15	176	88
6-8	0.482	0.104	1.5	3	5	0.075	0.15	138	69
6-11	0.408	0.088	1.9	6	5	0.095	0.3	92	29
12-14	0.255	0.055	1.9	6	5	0.095	0.3	58	18
15-18	0.214	0.046	1.6	9	5	0.08	0.45	58	10
19-50	0.271	0.058	2.6	11	5	0.13	0.55	45	11

In addition to manganese, other chemicals which are toxic by inhalation and relatively innocuous by the oral route are respirable crystalline silica, beryllium, and nickel.

Comment 9:

C. OEHHA Has Not Considered All of the Relevant Epidemiological Studies of Manganese, Nor Has It Considered Existing Benchmark Statistical Data for the 1992 Roels Study. Consideration of the Full Range of Studies Is Necessary to Ensure that the Manganese RELs Have Been Developed in a Scientifically Sound and Robust Manner.

OEHHA must consider "all available data" when it develops RELs.[55] In the case of the proposed manganese RELs, however, OEHHA has relied principally upon an epidemiological study conducted by Dr. Roels and his associates in 1992 without considering the full range of occupational studies that have been conducted for manganese before and after the 1992 study. Among the studies not considered by OEHHA are three particularly notable studies.

Two of the omitted studies concern a 1987 study also conducted by Dr. Roels on 141 male workers exposed to MnO_2, manganese tetroxide (Mn_3O_4), and various manganese salts (sulfate, carbonate, and nitrate) in a manganese oxide and manganese salts production facility. This study is important in an overall "weight-of-evidence" evaluation because the cohort investigated in the 1987 study was further evaluated by Crump and Rousseau more than ten years later. The significance of the follow-up study was that it evaluated a population that had experienced a chronic exposure to a relatively constant manganese air concentration, on average, over 14 years, and according to the authors, the manganese oxide workers demonstrated no significant progression of any previously reported impairment.

The third omitted study is a 1999 study conducted by Dr. Roels that reevaluated the cohort from the 1992 study on which OEHHA has based its proposed RELs. While not consistent across all endpoints, Roels and co-workers observed a complete reversal of one of the neurofunctional endpoints, even though these workers was still exposed to air concentrations of manganese well above 100 $\mu g/m^3$. These results suggest that, at least for one of the end-points evaluated (eye-hand coordination), there is a threshold dose below which the effect does not occur, and also that the effect of manganese on this particular parameter was reversible.

Considering the information provided in the four studies of two manganese oxide exposed cohorts provides the following information:

- High exposure levels caused workers to perform poorly on certain neuro-functional tests;
- The performance on these tests did not worsen with extended exposure durations; and
- The decrements in neurofunction were reversed when workers were removed from high manganese oxide exposures.

The extended exposure duration of the manganese oxide-/salt-exposed workers qualifies as a chronic exposure, and the study of the alkaline battery workers demonstrates both a lack of latency and, in some cases, a lack of persistency of the neurological effects. These updated studies indicate, at a minimum, that the uncertainty factor applied to the LOAEL to account for less than chronic exposure in the development of the proposed chronic manganese REL should be reconsidered by OEHHA. These and other pertinent epidemiological manganese studies not considered by OEHHA are described in more detail in Appendix 4.

OEHHA's new methodology for the derivation of non-cancer reference exposure levels also explicitly states that a benchmark dose statistical approach is preferred over the traditional NOAEL/uncertainty factor (UF) approach if sufficient data are available. Despite the clear preference for the benchmark dose statistical approach, OEHHA has not considered the substantial body of benchmark dose data available for the 1992 Roels study on which OEHHA has based its proposed manganese RELs.

> • In 2000, ATSDR issued a toxicological profile for manganese. The toxicological profile establishes a "minimum risk level" (MRL) for manganese relying upon benchmark dose statistical analyses of the raw data from the 1992 Roels study. (MRLs are comparable to the RELs developed by OEHHA.) ATSDR reported a NOAEL of 74 μg Mn/m³ from the 1992 Roels study using the benchmark statistical method (calculated as a "$BMDL_{10}$").
>
> • In 1996, the World Health Organization established an air quality guideline for manganese. The WHO manganese guideline is based on a benchmark statistical analysis of the 1992 Roels study. Consistent with the ATSDR assessment, the WHO reported a $BMDL_{10}$ of 74 μg Mn/m³ and a $BMDL_5$ of 30 μg Mn/m³.
>
> • In 1994, the U.S. EPA reported a wide range of benchmark dose analyses of the 1992 Roels study in connection with a manganese risk assessment completed at that time. The EPA analysis reported $BMDL_{10}$, $BMDL_5$, and $BMDL_1$ values for the 1992 Roels study using a range of different statistical assumptions. According to EPA, the most meaningful $BMDL_{10}$ values ranged from 72 to 118 μg Mn/m³, while the most meaningful $BMDL_5$ values ranged from 31 to 56 μg Mn/m³. The EPA analysis is summarized in the *U.S. Federal Register*.

OEHHA's proposed methodology states: "[I]n BMC determinations using human data, a case-by-case analysis is required" to select the appropriate benchmark dose of concern.[64] If OEHHA opted to use the same $BMDL_{10}$ from the 1992 Roels study that ATSDR used for derivation of the MRL, the chronic manganese REL would increase by a factor of three (even if further review of the available science did not prompt any other changes in the OEHHA analysis).

The proposed manganese RELs should be reconsidered, therefore, in light of the full range of available human epidemiological studies, as well as existing benchmark statistical data for the 1992 Roels study on which the proposed manganese RELs are based.

Response:

As stated above, OEHHA staff did not believe that other epidemiological studies of manganese that were completed before and after the study on which the proposed manganese RELs are based (i.e., Roels et al. 1992) provided the same level of detail for quantitative risk assessment as the Roels study. However we have included them in the revised REL summary for completeness.

With respect to ATSDR using a BMD analysis of Roels (1992) in the development of its MRL, it is interesting to note that the value they report (0.04 µg/m^3) is similar to the draft REL of 0.03 µg/m^3 developed in the REL. Nevertheless, if we use as our point of departure the BMDL$_{10}$ ATSDR used (0.074 mg/m^3), and apply the time adjustment they report (5d/7d, 8 hr/24 hr), a breathing rate adjustment of 10/20 for higher breathing rates from greater activity in the workplace, a subchronic UF of √10 for a study duration less than 12% of a lifetime, and intraspecies toxicokinetic and toxicodynamic UFs of 10 each, the estimated chronic REL would still be 0.03 µg/m^3.

Also, in regard to the benchmark analysis, we recently obtained the raw data from the Roels et al, 1992 study (thanks to USEPA for providing the raw data) needed to conduct the analysis made available to OEHHA. OEHHA calculated a BMCL from the raw data and used it to calculate 8-hour and chronic RELs of 0.36 and 0.13 ug/m3, respectively. These RELs are based on the best fit models for the most consistent adverse effects measured in Roels et al 1992, providing a BMCL05 of 109 µg/m^3. We applied UF's of √10 for a study duration less than 12% of a lifetime, and intraspecies toxicokinetic and toxicodynamic UFs of 10 each, for a total cumulative UF of 300. The toxicokinetic UF is in part to account for the 2-4-fold greater deposition of manganese particle in the airways of children and the lack of neonatal homeostasis, and the greater than 4-fold absorption of manganese from the intestinal tract compared with adults. The toxicodynamic UF reflects the potentially greater risk of neurodevelopmental damage from early life exposure...

Comment 10:

D. OEHHA Has Not Adequately Substantiated the Need for a 100-Fold Uncertainty Factor to Account for the Intraspecies Sensitivity of Infants and Children.

No compelling scientific data exist to justify the use of 2 uncertainty factors of 10 for intraspecies toxicokinetic (UF_{H-k}) and toxicodynamic (UF_{H-d}) uncertainties in the derivation of the RELs for manganese. The few studies cited by OEHHA to support their assertion of the need for a 100-fold uncertainty factor do not provide data that support conclusions about an increased sensitivity of infants and children to manganese. Appendix 5 evaluates the rationale provided by OEHHA for applying a 100-fold uncertainty factor and explains why the studies cited by OEHHA to support its rationale do not provide scientific justification for OEHHA's assertions. Appendix 5 also presents additional scientific information not considered by OEHHA when evaluating manganese exposure in infants and children and when selecting uncertainty factors for developing RELs for manganese.

To support the use of uncertainty factors for intraspecies toxicokinetic and toxicodynamic uncertainties, the studies would have had to address each of the following issues:

- Whether the route of exposure was comparable to any studies in adults;
- If data on exposure was presented in enough detail to compare to levels to which adults may have been exposed;
- If any of the endpoints evaluated in children were comparable to those examined for adults.

None of the studies cited by OEHHA have all of these essential elements. In addition, none of the studies provide information to support the reasons cited by OEHHA for an increased

susceptibility to manganese toxicity in infants: 1) greater gastrointestinal absorption; 2) inability to maintain homeostasis; and 3) an enhanced potential for manganese accumulation in the brain due to an immature blood brain barrier. Each of these parameters is a function of potential *toxicokinetic* differences that relate to how much of absorbed manganese is available for transport into the brain in an infant or child compared to adults. None of the studies cited, which included Wasserman et al. (2006), Takser et al. (2003), Collip et al. (1983), Zhang et al. (1995) and Ericson et al. (2007), evaluated manganese toxicokinetics, such as gastrointestinal absorption, homeostatis of blood manganese levels, or issues related to the integrity of the blood brain barrier in infants or children. Moreover, these studies cannot be used to assert that children are more susceptible to neurotoxicity than adults -- a toxicodynamic difference -- because none of the studies evaluated adults or compared their findings in children to studies conducted in adults with similar exposure and endpoints.

Response:

The Mn REL is based on healthy adult male workers with adjustments for the potentially greater susceptibility of children. As stated in the REL summary, the intraspecies toxicokinetic UF (UF_{H-k}) of 10 was chosen in part to reflect the 3-4-fold greater deposition of inhaled particulates in the 1-10 µm range in the lungs of neonates relative to adults exposed to similar particulate levels in ambient air (Ginsberg et al., 2005). It also reflects the 4-fold greater retention of manganese absorbed from the gut by neonates, and lack of homeostasis in the neonate. In addition, based on our interpretation of studies with neonatal and adult rats (Dorman et al., 2005), neonates accumulate higher levels of manganese in the brain more quickly than do adults with similar exposures. In Dorman et al. (2005), adult rats were exposed to 0.05, 0.5, and 1 mg/m^3 $MnSO_4$ for 28 days prior to mating, up to 14 days during the breeding period, 19 days during pregnancy, and 18 days during lactation. The pups were exposed during pregnancy, and during lactation, to the same air levels as the mother, as well as Mn in milk. Based on Figure 4 for the highest exposure, 1 mg/m^3, as measured on PND 19, Mn levels in <u>pup</u> striatum were ~0.96 µg/g (vs ~0.37 µg/g ctrl), and in cerebellum ~0.72 µg/g (vs ~0.34 µg/g ctrl). Based on Table 3 for the 1 mg/m^3 exposure on PND 18, Mn in <u>maternal</u> striatum was 0.89 µg/g, and 0.61 µg/g for cerebellum. Thus the pup to maternal Mn ratio was 1.1 in striatum and 1.2 in cerebellum. Thus available information indicates the use of a UF_{H-k} greater than the default value.

An intraspecies toxicodynamic UF (UF_{H-d}) of 10 was used to address the expectation that the still-developing brain of newborn and infant children is more sensitive to the effects of manganese and that injuries to the nervous system during development are anticipated to have lasting effects. This REL was developed with specific consideration of the potentially greater susceptibility of children to manganese neurotoxicity. Manganese neurotoxicity is only partially reversible in adults and it is likely that neonates and infants are more sensitive than adult workers. Further developmental neurotoxicity has been measured in children with elevated manganese exposures in drinking water, and elevated manganese levels in cord blood, hair and teeth. These studies are cited in the REL summary. Adults, by definition, cannot experience developmental neurotoxicity.

For comparison, the RfC for chronic manganese inhalation developed by the US EPA is 0.05 $µg/m^3$ (U.S.EPA, 1993), also based on Roels et al. (1992). Although they used a total

intraspecies UF of 10, they included a database UF of 10 due to a lack of developmental data, less than chronic exposure, and potential differences among various forms of Mn.

Comment 11:

E. Further Review of the Available Studies with Manganese Will Allow OEHHA the Opportunity to Consider Robust State-of-the-Art Scientific Developments Pertaining to Metals, Like Manganese, Which Are Both Essential and Potentially Toxic.

A number of scientific advancements pertaining to manganese are forthcoming in the very near future. Further review of the full body of manganese literature will allow OEHHA the opportunity to consider recent scientific developments and advancements.

1. Development of PBPK Manganese Models

The Hamner Institutes for Health Sciences will complete the preparation of four distinct PBPK models for manganese during 2008. The four PBPK models include: (1) an adult rat model; (2) an adult primate model; (3) a developmental rat model; and (4) a human model. All four models will incorporate olfactory nerve transport of manganese. An initial version of the adult rat model exists and is being refined at present. The other three models are scheduled for completion before the end of 2008.

The Hamner Institutes for Health Sciences will present the status of the PBPK models at a May 6-7, 2008 workshop scheduled to be held by the University of Ottawa's McLaughlin Centre for Population Health Risk Assessment (the Centre). The conference will focus on risk assessment for essential metals such as manganese, as well as copper and zinc. The Centre (and the Centre's director, Dr. Daniel Krewski) is well respected by the academic and regulatory communities, particularly in regard to risk assessment of metals. Materials from the workshop will be published in the *Journal of Toxicology and Environmental Health.* Probable workshop sponsors include Health Canada, the National Institute of Occupational Safety and Health ("NIOSH"), and EPA, as well as industry and academic institutions.

[A functional overview of a PBPK model for manganese is depicted in Figure 1.]

- **The biological plausibility of low inhalation exposures impacting tissue manganese levels can be explored using PBPK models.**

PBPK models can extrapolate to varying exposure conditions. They can therefore be used to determine quantitatively the contribution of inhaled manganese at environmental levels to blood and tissue manganese content. Initial results from the rat model parameterized to humans indicate that tissue accumulation of manganese in target brain tissues does not occur at low exposure levels (i.e. below 10 μg Mn/m^3) because manganese tissue levels are well-controlled until relatively high levels of exposure are reached (Figure 2):

[Figure 2 shows PBPK modeling results of mid-brain Mn accumulation following simulated chronic exposure to 0.001 to 10 mg/m^3 Mn..]

• PBPK models allow the use of more than one critical study to form the basis of a risk assessment.

PBPK models can be used to normalize various exposure and epidemiological studies on a dose to target tissue metric. In general, adverse effects within specific tissues are more closely related to the internal dose of a toxicant than the external concentration of the chemical in the environment. The ability of PBPK modeling to utilize numerous studies and evaluate internal doses to target tissues allows for a more robust risk assessment.

• PBPK models can be used to set the appropriate magnitude of adjustment factors instead of relying on uncertainty factors.

The ability to develop chemical-specific data instead of applying uncertainty factors is a key advantage PBPK models provide to risk assessment. For example, the PBPK models for manganese can be used to determine if an uncertainty factor to account for intraspecies variability in humans is appropriate or necessary. Further, these models can consider quantitatively the distribution of parameter values that can impact the accumulation and excretion of manganese. PBPK models can also be used to develop a range of estimated internal manganese doses for a population associated with a given exposure. In addition, the models can describe variation in tissue manganese levels at different life stages, including during potentially critical windows of susceptibility, such as early development. Further, the variation in manganese tissue levels can be described under both normal conditions and conditions of increased airborne manganese exposure. This powerful benefit of PBPK modeling allows risk assessors to determine the magnitude of any adjustment factors necessary to account for developmental concerns based on the contribution of inhaled manganese to developing offspring with greater accuracy and scientific justification.

• PBPK models allow a multimedia approach to risk assessment.

The PBPK models for manganese will be able to consider both ingested and inhaled inputs along with homeostatic controls in the derivation of RELs based on combined airborne and dietary exposures. In addition, incorporation of PBPK models for manganese in developing RELs would allow for the determination of the relative contribution of inhaled and oral manganese intake to tissue distribution; thus the relative risk of adverse effects from each route can be explored. The manganese PBPK model for humans, when complete, will be able to consider both ingested and inhaled inputs along with their controls to derive a REL based on airborne exposure along with dietary input. The use of PBPK models in a multimedia risk assessment for manganese would allow a sophisticated consideration of natural tissue manganese requirements and manganese homeostasis that a single media assessment, such as the risk assessment for manganese proposed by OEHHA, cannot duplicate. Application of PBPK models to a risk assessment of an essential yet toxic element has never been done because the models did not exist. While results are beginning to emerge (see Figure 2 and Appendix 2), the full suite of PBPK models will soon be complete, and use of these models for a manganese risk assessment will place OEHHA at the forefront by demonstrating the value and superiority of a multi-media approach and will allow for the development of scientifically robust RELs.

Response:

As stated above, OEHHA will review the PBPK models when made available in a final peer-reviewed document and the materials from the May 2008 workshop in Canada which are planned for publication in the Journal of Toxicology and Environmental Health. However, we are proceeding with development of the RELs for manganese.

Comment 12:

2. New Manganese Risk Assessments

In addition to the new OEHHA manganese risk assessment, several other regulatory authorities have indicated that they, too, are evaluating manganese. For example, Health Canada is expected to release a new manganese risk assessment sometime during 2008. Health Canada has reportedly obtained access to raw data from a separate study of occupational exposure to manganese overseen by Dr. Roberto Lucchini in Brescia, Italy. Health Canada reportedly conducted benchmark dose statistical analyses using the Lucchini data. How Health Canada's assessment of the Lucchini data differs, if at all, from its earlier assessment of the 1992 Roels study data is not yet known, but the existence of additional benchmark data may be of interest to OEHHA given OEHHA's clear preference in the new methodology for deriving reference exposure levels to use benchmark dose data "wherever available."

The Agency for Toxic Substances Disease Registry (ATSDR) has also recently issued notice that it intends to update its toxicological profile for manganese during 2008. Whether ATSDR has updated its benchmark analyses of the available occupational epidemiological studies of manganese is not known at this time, but, as in the case of the new Health Canada risk assessment for manganese, OEHHA might benefit from review of the assessment of its sister agency as it considers the science of manganese more comprehensively.

Finally, the U.S. EPA has also recently announced that it will update the risk assessment for manganese that appears on the Integrated Risk Information System (IRIS). During 2008, EPA will complete a literature review of the available manganese studies followed by development of one or more toxicity values.

Response:

OEHHA will review the new manganese risk assessments by Health Canada, ATSDR, and USEPA, when they are made available in final form. However, we are proceeding with the information we have available now to develop the manganese RELs.

Comment 13:

III. Further Review of the Manganese Science Is Necessary to Ensure OEHHA Is In Compliance with Its Statutory Mandates under California's Air Toxics Law.

The air toxics programs established by the California Legislature impose certain obligations on OEHHA as it works to implement those programs. For example, when conducting evaluations of the health effects of toxic air contaminants in California and when making any recommendations with respect to those toxic air contaminants, Health and Safety Code § 39660(b) requires OEHHA:

• to "consider all available scientific data;" and

• to use "current principles, practices, and methods used by public health professionals who are experienced in the fields of epidemiology, human health effects assessments, risk assessment, and toxicity;" and

Health and Safety Code § 39660(c)(1) further requires OEHHA:

• to "assess the availability and quality of data on health effects, including potency, mode of action, and other relevant biological factors, of the substance" in question.

Separately, Health and Safety Code § 44360(b)(2) specifies that "[h]ealth risk assessments required by [the Hot Spots program] shall be prepared in accordance with guidelines established by the Office of Environmental Health Hazard Assessment." OEHHA lacks the authority to take any actions governed by the foregoing statutory provisions without satisfying the core requirements of those provisions.

As explained in these comments, OEHHA has not considered all available scientific data relating to manganese. Nor has OEHHA adhered to current principles, practices, and methods for risk assessment. These principles, practices, and methods independently require consideration of all available scientific data, including "relevant biological factors" such as the essentiality of manganese for all age groups.

Finally, OEHHA must conduct its risk assessments for toxic air contaminants in accordance with guidelines prepared for that purpose by OEHHA. In addition to OEHHA's failure to consider all of the relevant science concerning manganese, OEHHA has not adhered to its own newly proposed methodology in several notable respects.

• First, the new methodology for the derivation of non-cancer reference exposure levels explicitly states that a benchmark dose statistical approach is preferred over the traditional NOAEL/uncertainty factor (UF) approach whenever sufficient data are available.[70] Despite the clear preference for the benchmark dose statistical approach, OEHHA has omitted any consideration of the substantial body of benchmark dose data available for the 1992 Roels study on which OEHHA has based its proposed manganese RELs.

• Second, the new methodology requires application of "default" uncertainty factors in the absence of data requiring application of different uncertainty factors. One such default uncertainty factor is a factor of $\sqrt{10}$ where insufficient data exist to address intraspecies toxicodynamics. Despite the clear directive to use default uncertainty factors, OEHHA has opted to increase the uncertainty factor for intra-species toxicodynamics to 10 for manganese without any detailed scientific explanation of the basis for the enhanced uncertainty factor. Appendix 5 provides a detailed explanation for why a 100-fold uncertainty factor to account for intraspecies toxicokinetics and toxicodynamics uncertainty is not warranted.

• Third, OEHHA's new methodology for noncancer risk assessment states that no uncertainty factor is necessary where the critical studies have exposure durations that are greater than 12% of a typical lifespan. Although the 1992 Roels study did not have the requisite exposure duration, a subsequent study of the 1992 Roels study cohort (together with an earlier companion study conducted by the same investigator) not considered by OEHHA clearly expand the exposure duration.

Illustrating the practical importance of these alterations from OEHHA's proposed methodology, *reliance upon the available benchmark data and default uncertainty factors would result in the derivation of a chronic manganese REL thirty times higher than the REL proposed by OEHHA as shown below*:

Study	Roels et al. 1992; Roels et al. 1999
Study population	102 workers in a battery plant
Exposure method	Inhalation of workplace air
Exposure continuity	
Exposure duration	8 hr/day, mean exposure 14+ years (greater than 12% of estimated lifespan)
Critical effects	Impaired neurobehavior: visual reaction time, eye-hand coordination, hand steadiness
LOAEL	0.15 mg/m³
NOAEL	Not observed
Benchmark concentration	0.074 mg/m³ ($BMDL_{10}$)
Time-adjusted exposure	0.026 mg/m³ (0.074 mg/m³ x10/20 x 5/7)
LOAEL uncertainty factor (UF_L)	Not applicable
Subchronic uncertainty factor (UF_S)	1 (study duration > 12% of estimated lifespan)
Interspecies uncertainty factor	
Toxicokinetic (UF_{A-k})	1 (default: human study)
Toxicodynamics (UF_{A-d})	1 (default: human study)
Intraspecies uncertainty factor	
Toxicokinetic (UF_{H-k})	10 (greater lung deposition in children)
Toxicodynamics (UF_{H-d})	$\sqrt{}$ 10 (greater susceptibility of children to neurotoxicity)
Cumulative uncertainty factor	30
Reference Exposure Level	**0.9 µg/m³**

Response:

OEHHA has reevaluated the Mn RELs in the light of these and other comments. We disagree with the commenters assertion that we have not evaluated all available information. As we have stated in the tSD, we do not provide an in-depth summary of every study in the REL, but rather focus on those studies key to development of the REL. Further, wehave developed a revised REL based on a benchmark dose analysis in the revised TSD. We chose different uncertainty factors than the commentator chose in their above example . The current RELs are described in response to comments above and can be viewed in the revised TSD.

Comment 14:

Conclusion

MIG appreciates the opportunity to provide comments on this important OEHHA proposal. Review of all of the relevant science for manganese will ensure that the manganese RELs are scientifically sound and protective of public health, including the health of infants and children.

Response:

OEHHA thanks MIG for its extensive comments. As noted, we have revised the REL using a benchmark dose methodology.

Comments of Gina M. Solomon, M.D., M.P.H. and Miriam Rotkin-Ellman, M.P.H., on behalf of the Natural Resources Defense Council.

Introduction

We appreciate this opportunity to submit comments on behalf of the Natural Resources Defense Council (NRDC), a non-profit organization with over 1.2 million members and activists, 250,000 of whom are Californians. NRDC has no financial interest in any of the chemicals subject to the current comments. NRDC members in California live in communities where they and their children face exposures to air toxics. We hear serious concerns from our membership about the particular risks to children from air pollution, and about the disproportionate risks faced by children with asthma. NRDC supported the Children's Environmental Health Protection Act of 19991 because we are aware of the scientific evidence showing that children are more exposed to toxic air pollutants, and they are more susceptible to many of the health effects from chemical pollutants. We are concerned that current regulatory standards, set with the goal of protecting adults, may not adequately protect children from these serious environmental hazards.

OEHHA is required to develop guidelines for conducting health risk assessments under the Air Toxics Hot Spots Program (Health and Safety Code Section 44360 (b) (2)). These documents were most recently updated in 1999-2000, and there is once again a need to update risk assessment methods to reflect the significant advances in the science since that time. In accordance with the mandate of the Children's Environmental Health Protection Act, OEHHA is also required to include in these guidelines consideration of the differential effects on the health of infants, children and other sensitive subpopulations.

The OEHHA draft technical support document, and the specific Reference Exposure Levels (RELs) derived for acetaldehyde, acrolein, arsenic, formaldehyde, manganese, and mercury, are generally well-supported scientifically. We believe that these form a solid foundation for updating the RELs for other air toxics, and we strongly agree that acetaldehyde, arsenic, formaldehyde, manganese and mercury should all be promptly listed under SB 25 as chemicals which disproportionately impact children (Health and Safety Code, Section 39699.5). NRDC also supports the derivation of 8-hour RELs. We frequently encounter situations involving exposures at schools, day care centers, or other settings where 8-hour RELs are appropriate benchmarks for comparison. We look forward to having 8-hour RELs available for use in such situations in the future.

Our comments focus on the rationale and magnitude of some of the uncertainty factors (UFs) that OEHHA proposes in the draft guidelines for deriving RELs. We are concerned that in several cases the approach described in the guidelines does not provide an adequate margin of safety to protect the health of infants, children, and other sensitive populations. We also provide specific comments on the proposed RELs for mercury and manganese.

Comment 1: Uncertainty Factors are Designed to Protect Sensitive Populations

Uncertainty factors are often a source of some disagreement because they rely on a combination of scientific justification and policy judgment to adjust a point of departure downward to a REL. If the UFs are excessive, there is some cost to industry and society. However if the UFs are insufficient to protect health with an adequate margin of safety, people could be sickened or injured simply from breathing the air where they live or work. Therefore we strongly believe that it is far better to err on the side of safety in the derivation and use of uncertainty factors. In several cases we believe that OEHHA does not incorporate an adequately health-protective approach.

Response:

OEHHA agrees that the value chosen for uncertainty factors in any risk assessment should be sufficient to ensure that the resulting REL should be protective of the exposed population. The concern as to the cost to society is not directly involved in REL derivation, but there is a need for scientific justification and consistency. If these objectives are met, the risk managers will be able to address cost/benefit considerations fairly and effectively. In particular the value of the UF_H *used should be sufficient to cover the range of sensitivities anticipated, including sensitive subpopulations. The default values recommended in the guidelines may not need to include extreme values identified for a few highly exceptional chemicals whose special properties are known to be unique, but should certainly cover the likely range predicted for most chemicals in the absence of more specific information. OEHHA has generally used a 95% confidence bound as a reasonable standard in setting the default values for uncertainty factors, although obviously this is harder to apply systematically when dealing with uncertainty as opposed to variability. In particular cases where a larger uncertainty factor is considered appropriate based on chemical-specific information, this larger factor will be used instead of the default, as is seen in some of the example REL derivations.*

Comment 2: LOAEL-to-NOAEL Factor Should Not Be Reduced for So-Called "Mild Effects"

We support preferentially using a benchmark dose (BMD) approach instead of the NOAEL approach whenever the data permit. However, in many cases there are insufficient data to support using a BMD approach or deriving a NOAEL. One critical uncertainty in the derivation of several RELs according to the draft guidelines is the LOAEL to NOAEL extrapolation. In these cases the scientific research has failed to uncover a dose that does not cause an adverse effect. This situation is particularly worrisome because there is no way of knowing how much lower the level of concern really lies. An UF of 10-fold has traditionally been used in this type of situation. We are very concerned that OEHHA proposes in the draft guidelines to reduce this to only 6-fold in the case of a "mild effect". Worse still, the definition of a "mild effect" is undefined and unjustified scientifically.

The implications of this ill-considered decision become clear in the case of manganese, where the 8-hour and chronic RELs are both derived from a study of battery plant manufacturing workers (Roels et al, 1992). These workers were found to have significant (although subtle) neurobehavioral effects at the lowest exposure levels. We are shocked that OEHHA classified

highly significant deficits in hand-eye coordination, delayed reaction time, and hand tremors as "mild effects". Manganese is known to cause Parkinsonian-like brain damage, and early signs of such damage are clearly apparent in the battery manufacturing workers studied by Roels et al. These are hardly what any reasonable person would classify as "mild effects". These effects are reminiscent of those seen in lead industry workers decades ago when the low-level neurological effects of lead were still poorly understood. We are alarmed that OEHHA has created this poorly-justified category and is already reducing the critically-important LOAEL-to-NOAEL UF based on weak or absent scientific justification.

NRDC strongly urges OEHHA to use at least a full 10-fold UF in all cases. If OEHHA chooses to retain a "mild effect" category, such a category should never include neurological, developmental, endocrine, or other effects that are likely to be progressive and may not have a threshold. Specifically, in the case of manganese, we believe OEHHA is obligated to use at least a full 10-fold UF for the LOAEL-to-NOAEL extrapolation.

Response:

OEHHA appreciates this comment as it points to internal inconsistencies in our Technical Support Document, as well as a rethinking about how we think of the LOAEL to NOAEL extrapolation, and how it was applied in our example RELs. The document was confusing in using the terms mild effect differently in different places, and in what we meant by a "mild" effect in this contex. We revised the discussion of the LOAEL to NOAEL Uncertainty Factor, or UF_L, in the technical support document. In the context of UF_L OEHHA is not making a judgment about the nature of the critical effect – what might be termed "seriousness" of the endpoint. The purpose of UF_L is to allow for the estimated ratio of the observed LOAEL to a hypothetical NOAEL which was not observed in the study, but could have been observed if the study design had included additional dose levels. This concept has been used for many years in U.S. EPA risk assessments, and was carried forward from the previous version of the OEHHA guidelines without modification. As developed in considering acute endpoints, the contrast between a "mild" and a "severe" response is a distinction based on the degree of response at a single target site or organ. Thus the different levels of response in Table 5.5.1 (adapted from U.S. EPA) represent different grades of histological damage, or different degrees of the same physiological or biochemical response. In particular, there is no explicit attempt to compare different endpoints by this distinction. The underlying assumption is that a dose level which produces a severe grade of toxic response is likely to be further away from the NOAEL for that endpoint than a dose level which produces only a mild degree of toxicity.

We have reconsidered the application of this distinction between gradation of effect for the LOAEL to NOAEL ratio for chronic effects. The categorization of responses into a sequential series of severity grades has not been found to be helpful for repeated or chronic exposuresl; as noted in this comment, many chronic effects might be considered "severe" at any response level. Also, the concept of reversibility, used in defining acute severity, has limitations in the context of a long-term continuous exposure, which is the case for exposure to facility emissions. For chronic exposures, therefore, the document has been revised and we have reverted to our previous guidance on whn it may be appropriate to use a UFL less than 10. For example, a low percentage of responders,may indicate that the LOAEL is closer to a NOAEL than 10 fold, particularly for a steep dose-response curve.

In the case of manganese, the question is whether the effects seen are mild manifestations of a serious effect (e.g. neurotoxicity). In the example of the study by Roels et al. (1992) on manganese, follow up studies after 11 years with this same cohort indicated that many, but not all, of the initially observed effects either abated with time or did not progress to clinically identifiable signs (Crump and Rousseau, 1999). The choice of a value for UF_L in this case is a difficult one, and hinges on the percentage of exposed individuals showing a consistent response. However, OEHHA does consider neurotoxicity to be a serious concern, and one which may have a differential effect on infants and children as indicated by the use of a larger-than default UF of 10 for intraspecies toxicodynamic variability. Finally, OEHHA has revised the manganese REL so as to avoid the difficult choice of a proper value for UF_L, and also remove the uncertainty associated with extrapolation from the LOAEL, by obtaining original data (not presented in the published paper) which allow application of benchmark concentration methodology to the data from Roels' study.

Comment 3: Replacing Protective Uncertainty Factors with PBPK Models is Often Premature

Physiologically-based pharmacokinetic modeling (PBPK) has the potential to better incorporate scientific data and to reduce uncertainty in deriving RELs from animal data. However, except in unusually data-rich circumstances, we have serious concerns about using such models to replace UFs. For example, the U.S. EPA completed a draft cancer risk assessment of the data-rich chemical trichloroethylene (TCE) and attempted to use two different PBPK models to derive a cancer risk.2 The Science Advisory Board committee commented in general support of the concept of using PBPK modeling, but raised concerns about the fact that there was a 19,600-fold difference in the 95% CI span between the Clewell et al. and Fisher et al. PBPK models.3 Rather than reducing uncertainty, modeling approaches have the potential to magnify uncertainty. Depending on the assumptions underlying the model, the result can be more or less protective of public health. In addition, because these models are difficult for the public to adequately understand and critique, the result can come to resemble a "black box" approach to risk assessment. If the public does not trust the modeling results and cannot penetrate the model to critique it, the public will increasingly be shut out of the risk assessment process and will be less and less likely to trust the outcome. Finally, extensive modeling is time- and resource-intensive for OEHHA, and will tend to delay the promulgation of RELs. This trade-off in efficiency is unlikely to be worthwhile in most circumstances given the real limitations on Agency time and resources.

NRDC urges OEHHA to seriously consider the adequacy of the database and to use modeling only when it is clear that the scientific foundation is unusually strong and the benefit in refining the risk assessment is unusually compelling. In most situations, it is far preferable, less open to criticism, and more efficient, to use a standard 10-fold UF for the toxicokinetic component of the interspecies UF.

Response:

OEHHA agrees that not all proposed PBPK models are helpful, and does not intend to use such models without adequate supporting data and validation. We are aware of the extreme variation in predictions for the various trichloroethylene models, although we view this as an unusual case

reflecting disputes or uncertainties about toxicodynamics as well as toxicokinetics of trichloroethylene. In general, OEHHA disagrees with the view that "modeling approaches have the potential to magnify uncertainty". Rather, it is considered that these approaches reveal and to some extent quantify uncertainty which was always implicitly present. Nevertheless, OEHHA takes note of the concerns expressed in this comment. We will try to avoid these problems as far as possible, while still using PBPK and other modeling techniques when scientifically justified and effective in reducing uncertainty.

Comment 4: Database Deficiencies can be Dangerous

It is shocking and potentially dangerous that significant gaps so often exist in the scientific literature on highly toxic substances. With such database deficiencies there is a significant threat of missing undefined risks that could completely change the establishment of safe levels. Therefore, it is important for regulatory agencies such as OEHHA to respond to data deficiencies by imposing a significant precautionary uncertainty factor until the deficiency is remedied. The factor should be sufficient to account for the possibility that there is significant undefined developmental toxicity, neurotoxicity, endocrine disruption, immunotoxicity, or other effects that have not been assessed.

It is surprising that OEHHA proposes to use a database deficiency UF of only 3-fold ($\sqrt{10}$) to account for "substantial data gaps" including the absence of developmental toxicity studies. There is no scientific justification for this proposal, and it is reckless and inadequate to use a default factor that is so meager to protect people exposed to toxic air contaminants. It is hardly reassuring to communicate to affected communities that nothing is known about whether the chemical may affect their children's development, their brains, or their hormones; and that OEHHA has divided the "safe dose" by three and thinks that this may adequately protect them.

NRDC notes that a minimum default database UF of 10-fold is historically justified in similar circumstances and has been used by U.S. EPA. We strongly urge OEHHA to use a default database UF of 10; such a factor could be adjusted downward if there is a strong suggestion that the uncertainty is unlikely to be significant.

Response:

OEHHA agrees that a UF_D of 10 may be justified in some cases, although it should be noted that in U.S. EPA risk assessments some of the database uncertainties which they address by this factor may be included in the increased value of $UF_{H\text{-}k}$ proposed by OEHHA. We intend to rewrite this section of the TSD to indicate that the value of this uncertainty factor could be chosen as either 10 or $\sqrt{10}$ depending on the specific case, and also to clarify the circumstances in which it should be applied. It is intended that this factor may also be used to address data deficiencies other than lack of developmental toxicity data, although this is likely to be a frequent case where it is applicable.

Comment 5: Need for a Children's Uncertainty Factor

The National Academy of Sciences (NAS) affirmed in 1993 that children have greater potential susceptibility to the toxic effects of pesticides, including their effects on the developing nervous,

immune and reproductive systems[4]. This susceptibility stems from both a fetus or young child's potential for greater inherent sensitivity to pesticides and other toxic chemicals, due to rapidly developing cells and organs, as well as from a child's greater exposures. In the same study, the NAS recognized that existing pesticide data requirements and toxicity testing failed to generate certain data critical to the characterization of children's risk from toxicity and exposure to pesticides. We are pleased that OEHHA has made major strides toward incorporating children's susceptibility into the new draft guidelines and we support the general approach of designing RELs that will protect children. However, we believe that OEHHA could go one step further in incorporating a child-protective margin into RELs.

As a result of the NAS report, Congress unanimously passed the Food Quality Protection Act (FQPA) of 1996. Section 408 of this law requires that "an additional tenfold margin of safety for the pesticide chemical residue and other sources of exposure shall be applied for infants and children to take into account potential pre– and post–natal toxicity and completeness of the data with respect to exposure and toxicity to infants and children." The FQPA also explains that the Administrator may use a different margin of safety "only when, on the basis of reliable data" the alternative will be safe for infants and children. (FFDCA sect. 408 (b)(2)(C)).

As a result, for pesticides, U.S. EPA is required to use separate UFs for intraspecies variability and for children's susceptibility, thereby resulting in a combined UF of up to 100-fold. OEHHA is proposing to take a considerably less precautionary approach than Congress mandated of EPA. Specifically, OEHHA proposes to subdivide the intraspecies UF into two factors – for pharmacokinetics and pharmacodynamics – and then to allow for a potential child-protective factor as part of the former. This could result in a combined UF of up to 30-fold – considerably less than suggested by the NAS and mandated for pesticides by Congress. Not only is the proposed approach less health-protective than we believe is warranted, it also is more complex than generally substantiated by the science. OEHHA admits that "Differentiating the contribution of toxicokinetic (TK) and toxicodynamic (TD) differences is difficult." (ES p. xiii). OEHHA further acknowledges that "there are scant data available to indicate whether or not the toxicodynamic subfactor of $\sqrt{10}$ adequately protects infants and children." (ibid). Yet in the same paragraph, there are three examples of toxicants for which toxicodynamic factors render children many-fold more sensitive than adults. More striking still, one of the three toxicants highlighted in this example (mercury) is one of the six chemicals for which OEHHA derives a REL in this document without adequately incorporating children's toxicodynamic sensitivity (see below).

NRDC urges OEHHA to simplify the process by using a single factor to account for intraspecies differences, and to incorporate an additional child-protective factor with a default value of 10-fold "to take into account potential pre– and post–natal toxicity and completeness of the data with respect to exposure and toxicity to infants and children".

Response:

OEHHA disagrees with the argument that a single additional factor to protect infants and children is more scientifically justified than adjustments to the specific factors or subfactors addressing different sources of uncertainty in relation to age-related kinetics and susceptibility. The recommendation of the NAS and requirement by FQPA of an adjustment factor to allow for effects of pesticides on infants and children is not strictly comparable to the inhalation exposures

to industrial and environmental chemicals considered here (and is not used by U.S. EPA in this context at the present time). The chemicals and toxic endpoints are different, and in many cases (e,g., neurotoxicity) fall into a class to which OEHHA intends to give special consideration. The FQPA factor also includes consideration of uncertainty about exposure assessment for children. For oral exposures, differences in intake rates and other exposure-related parameters would be addressed as part of the exposure assessment phase of a Hot Spots risk assessment. The effect of intake rates on inhalation exposures is complex and depends on the chemical: in our proposed methodology it may be addressed by specific models in cases where the impact is greater than is allowed for by the default uncertainty factor. Finally, U.S. EPA's Office of Pesticide Programs does not apply the FQPA factor as an across-the-board tenfold adjustment, but has developed a guidance document laying out considerations and methods for determining whether such an adjustment is in fact necessary and, if so, what its magnitude should be (Determination of the Appropriate FQPA Safety Factor(s) in Tolerance Assessment. Office of Pesticide Programs, U.S. Environmental Protection Agency. Washington, DC, February 28, 2002). In view of the complexities which U.S. EPA has faced over the application of the FQPA factor or other similar adjustments, we expect that our more case-specific approach will prove more scientifically defensible. Finally, we do apply a UF of up to 10 for toxicodynamic differences where this is justified by the data, as we did with manganese. We revised the methods description to clarify that this increased toxicodynamic factor is an option.

Comment 6: Limit on the Aggregate Uncertainty Factor Should be Discarded

We were disturbed to see the statement that "The product of all UFs applied usually will not exceed √10 x 103 (or 3000 after rounding to one significant figure). ES p. xiii. This artificial "cap" – if used to eliminate needed UFs – will virtually guarantee that susceptible populations and children will not adequately be protected from toxic air contaminants. It would be scientifically unjustifiable were OEHHA to choose not to incorporate an UF in order to avoid exceeding an aggregate of 3000-fold. This type of uncertainty factor shell-game implies that the UFs can be manipulated to stay below a predetermined total. For example, the implication is that OEHHA might choose not to use a database UF even if there were no data on developmental toxicity in a chemical that is likely to be a significant risk to children, just to stay below the magic total of 3000.

NRDC believes that a cap on the total uncertainty is scientifically unjustifiable and inappropriate. No predetermined cap should be set.

Response:

The application of an upper limit of 3000 for the total UF has been used previously by both U.S. EPA and OEHHA, most often as an indication that if a larger overall uncertainty factor than this was required the reliability of the assessment was questionable. OEHHA continues to be concerned that this may apply where very large cumulative uncertainty factors are indicated. However, as stated in the TSD, it is not intended that this restriction be regarded as absolute, and there may be cases where an overall UF greater than 3000 will be used.

Comment 7: Mercury REL Requires Database and/or Larger Toxicodynamic Uncertainty Factor

Mercury is an important example of a chemical with a critical data gap. Surprisingly, OEHHA fails to address this data gap with even the inadequate UF of √10 that is presented in the guidelines. Mercury, in all of its bioavailable forms, is a known neurotoxicant. In some of its forms (eg. organic mercury) it is an exceptionally potent developmental toxicant that is known to cause permanent damage to the developing human brain. Elemental mercury is known to readily cross both the placenta and the blood-brain barrier. Animal studies summarized in the draft mercury REL have shown that the targets of methyl mercury and elemental mercury are similar or identical in the central nervous system; these studies have also shown that the developing animal is at greater risk of neurological impairment. There is therefore ample reason for concern about the neurodevelopmental effects of airborne elemental mercury.

There are no human epidemiological studies incorporating developmental exposures to elemental mercury, so OEHHA chose to use a study of adult workers. The database does not contain adequate information about the developmental neurotoxicity of elemental mercury and therefore the guidelines call for an additional database UF of at least 3-fold. The use of the full 10-fold factor for toxicokinetic susceptibility in children is in no way adequate to address this problem, as the issue is not with toxicokinetics but rather with toxicodynamics (greater susceptibility of children to neurotoxicity) and database insufficiency. We strongly urge OEHHA to incorporate an additional database UF of 3-10 fold to protect against developmental neurotoxicity to children. Alternatively or in addition, OEHHA could incorporate a toxicodynamic UF of 10-fold to account for the likelihood that children are more susceptible to mercury neurotoxicity.

Response:

OEHHA agrees with the assertions above that elemental mercury is of serious concern as a neurodevelopmental toxicant, similar to methylmercury. We also concur that the issue is one of toxicodynamics rather than toxicokinetics. For these reasons, an intraspecies toxicodynamic UF of 10 was applied for the 8 hour and chronic RELs to account for the greater susceptibility associated with early life exposures to mercury. The reason we did not apply the 10 fold UF for toxicodynamics to the acute REL is because the basis of the acute REL is a developmental toxicity study in rats.

While there are few neurodevelopmental studies of elemental mercury, it appears unlikely from the extant studies that the neurotoxic effects of elemental mercury will be substantially different from those of methylmercury with regard to age-related differences in susceptibility, although there are differences in the toxicokinetics of these different chemical forms. This apparent similarity between elemental and methylmercury, for which a more extensive database on neurodevelopmental effects exists, suggests that an additional database deficiency factor is not necessary.

Comment 8: Manganese REL is Inconsistent with the Mercury REL

In marked contrast with the failure to include toxicodynamic susceptibility of children to neurotoxicants in the mercury REL, OEHHA appropriately included a full 10-fold UF in the

REL for manganese to address just this concern. Like elemental mercury, manganese is a neurotoxicant with chronic effects in humans. Again, OEHHA chose to use a study of adult workers for derivation of the REL. However, the risk assessments diverge in the selection of UFs, and the differences are not adequately explained. While the neurological effects of mercury are not classified as "mild" (and could never be classified as such), OEHHA inexplicably classifies the equally significant adverse neurological effects of manganese as "mild". Such a classification is totally unjustifiable scientifically and should be abandoned, as stated above. OEHHA did, however, directly acknowledge the fact that children have both toxicokinetic and toxicodynamic susceptibilities to neurotoxicants. Such an assumption is well-justified on the basis of other common neurotoxicants such as lead, mercury, and organophosphates, for which the toxicodynamic susceptibility of children is well-established. In addition, there is some direct evidence that such toxicodynamic susceptibility applies for manganese as well. Thus there is a sound basis for including a full 10-fold UF here. Such an UF can be readily justified in general to protect children, as stated above.

Response:

Please refer to the earlier discussion (in response to Comment 3) for explanation of our use of the term "mild effect" in the context of the LOAEL to NOAEL extrapolation. We have revised the TSD to clarify what we mean in the context of acute RELs by severity of effect and to change the application of this concept to 8-hour and chronic RELs The LOAEL to NOAEL conversion uncertainty in the Roels et al. (1992) study of manganese exposed workers is a particularly difficult question, which we answer in a revised version of this derivation. We were unable to use benchmark concentration methodology with the data as published in the original paper, but we have now obtained the original source data, which can be used in the benchmark concentration analysis. These were previously provided to U.S. EPA. Use of a benchmark concentration calculation avoids the necessity of a LOAEL to NOAEL uncertainty factor.

The different values for the other uncertainty factors for mercury and manganese reflect a number of differences in nature of the exposures and the mechanisms by which these metals cause neurotoxicity. For instance, the toxicokinetics for exposure to elemental mercury (a vapor) are likely to be simpler, and less variable, than those for exposure to particulate manganese compounds. Whereas mercury adversely affects several organs in addition to the brain, there is a larger uncertainty regarding what portions of the brain are affected and how. In contrast, a reasonably large body of data indicates that manganese accumulates in dopaminergic neurons and especially in the extrapyramidal system.

With significant manganese exposure, the symptoms of frank manganism are seen, including widespread rigidity, tremor, dystonia and, possibly, dementia. The measured effects of decreased visual reaction time, poorer eye-hand coordination, and hand steadiness reported by Roels in the critical study, are less severe, although by no means insignificant. As noted in response to comment 3, we did not mean to imply that neurotoxicity is not a serious outcome. Rather, in the original derivation of the manganese REL we chose a LOAEL to NOAEL uncertainty factor of 6 based on the percent of workers (≤ 30%) responding with relatively mild neurotoxicity under the workplace exposures, which appeared at least based on a follow-up study to be reversible. However, we are revising this REL because we now have the original data and can conduct a benchmark concentration analysis, thus avoiding the LOAEL to NOAEL

extrapolation altogether. Also, as noted earlier, we are revising our discussion of that particular uncertainty factor to reflect our current thinking as we applied it to the sample RELs.

Comments of Mike Dourson and Melissa Kohrman, on behalf of Toxicology Excellence for Risk Assessment (TERA).

Comment 1:

TERA would like to thank OEHHA for providing the opportunity to review the draft Technical Support Document for the Derivation of Noncancer Reference Exposure Levels provided by the Air Toxicology and Epidemiology Branch. The overall goal of this work is admirable and we appreciate the agency's concern for children's health and developmental risk.

TERA has, however, some of concerns about using an uncertainty factor greater than 30 for intraspecies variability. We feel that there was not sufficient discussion as to why the current default uncertainty factor does not effectively protect children or other subpopulations susceptible to developmental effects. It is our understanding that an uncertainty factor of 10 takes these sensitive subgroups into account and adequately protects them and that an uncertainty factor of 30 would be overprotective and overconservative.

For example, OEHHA states:

> When an uncertainty factor approach is used due to the lack of data for compound-specific models of toxicokinetics and toxicodynamics, an overall intraspecies uncertainty factor (UFH) of 30 rather than 10 (toxicokinetic component, UFH-k =10; toxicodynamic component, UFH-d = ?10) will be used as a default procedure to protect infants' and children's health in cases where metabolism is important in the activation or elimination of the compound and where renal and hepatic activity is key to the toxicological activity. For direct-acting chemicals whose site of action is the point of first contact a UFH-k of ?10 may be sufficient. Where significant concern for toxicodynamic differences larger than three-fold is present, a larger UFH-k may be applied.

The description above seems to be missing supporting information. For example, Dourson et al. (2002) look at essentially the same question, based in part on the work of Scheuplein et al. (2002), and concluded that the uncertainty factors for within-human variability and database completeness were more than sufficient to protect children and infants in general, but that specific data could (and should) be used to replace such default factors when appropriate. Our OEHHA colleagues would benefit from a similar analysis, or at least a reading of the Dourson et al. (2002) paper.

References:

Dourson, M.L., G. Charnley and R. Scheuplein. 2002. Differential Sensitivity of Children and Adults to Chemical Toxicity: II. Risk and Regulation. Reg. Tox. Pharmacol. 35:448-467.

Scheuplein, R., G. Charnley and M.L. Dourson. 2002. Differential sensitivity of children and adults to chemical toxicity: I. Biological Basis. Reg. Tox. Pharmacol. 35:429-447.

Response:

> *OEHHA is of course familiar with the publication by Dourson* et al. *(2002) and Scheuplein* et al. *(2002), but does not regard these as consistent with more recent work on the subject of*

uncertainty and variability in human response. Dourson et al. *(2002) presented an extensive analysis essentially defending the current UF_H as being adequate for all members of an exposed population including children and infants. In their Table 3 they present a list of U.S.EPA RfD's presumably indicating the adequacy of UF_H values of 10 or less over a wide range of chemicals. OEHHA's specific concern is that in the case of neonatal and young infants, the UF_{H-k} of √10 is probably inadequate for inhalation exposure. A number of published analyses of human data and predictions from modeling indicate that an increase of the UF_{H-k} to 10 would be prudent in those cases where insufficient data are available. For example, the following studies support OEHHA's proposal. A limitation of the available data is that relatively few studies have focused on inhalation exposure and predictive PBPK analyses have limitations as well.*

Renwick (1998) and Renwick et al. (2000) compared age-related differences in the pharmacokinetics of 36 drugs which are eliminated by different processes. Renwick et al. (2000) concluded that the main factor affected by age was the overall difference in clearance and the resulting elevated internal dose in neonates and children compared to adults. While these authors concluded that a UF_H value of 100 was not justified, they noted that an additional factor (>10) might be necessary in the case of a lack of developmental and reproductive toxicity data, inadequate data, or an irreversible toxic effect in neonates/young animals.

Dorne et al. (2001) evaluated the validity of the √10 UF_{HK} in relation to CYP1A2 metabolism using published data for clearance (CL), AUC and peak plasma concentration (Cmax) for caffeine, theophylline, theobromine, paraxanthine, and R-warfarin in human volunteers. The authors identified subgroups for which the √10 would be inadequately protective including about half of pregnant women, nearly all neonates, and 13% of infants. These drugs were administered orally or parenterally.

Ginsberg et al. (2002) also evaluated child/adult pharmacokinetic differences in the drug literature. These authors identified about 100 chemicals with some pharmacokinetic data and analyzed a subset of 45. Multiple regression analysis was used to evaluate relationships between age groups and mean pharmacokinetic parameter (Cmax, half-life, AUC, volume of distribution, clearance). In general, for many chemicals, early life stages appeared different in terms of clearance, half-life, and volume of distribution. The overall study results indicate that premature and full-term neonates tended to have 3 to 9 times longer half-life than adults for the drugs studied. Like the earlier work of Renwick et al. (2000) and Dorne et al. (2001) the drugs studied were administered orally or parenterally, not by inhalation.

Pelekis et al. (2001) used a PBPK model to derive adult and child pharmacokinetic UFs for a group of volatile organic compounds (VOCs). Adult models (50 and 90 kg) were compared with a 10kg child model. Simulations involved continuous exposure to 1 ppm VOC for 30 days. Arterial, venous and tissue concentrations of the parent VOCs were used to calculate Adult/Child values. For the Liver concentration metric the Adult/Child values were: styrene (0.033); xylene (0.037); trichloroethylene (0.061); dichloromethane (0.092); and chloroform (0.11). The model predictions indicate up to a 30-fold higher concentration of VOCs in child liver than adult liver. Unlike the drug studies above this modeling study involves inhalation exposure of relevant environmental toxicants.

Jonsson and Johanson (2001) used a PBPK model of dichloromethane (DCM) to study the influence of metabolic polymorphism on cancer risk estimates. Exposure was by inhalation and metabolism by glutathione transferase theta (GSTT1) and mixed function oxidases (MFO) occurred in lung and liver. The model was fitted to published toxicokinetic data on 27 male volunteers exposed to 250-1000 ppm DCM. Excess cancer risk resulting from lifetime exposures to 1-1000 ppm DCM was estimated using Bayesian and Monte Carlo methods. The relevant dose metric was DNA-protein cross links (DPX) in liver derived from DCM metabolized via the GSTT1 pathway. Data on the frequencies of the three GSTT1 genotypes (0/0, +/0, +/+) in the Swedish population were used in the analysis. The results indicated a large interindividual variability in estimated risk, even within the two metabolizing groups (+/0, +/+). The results indicate that the UF_{HK} of √10 for human PK variability may not be adequately protective for non-cancer endpoints. One percent of the population would not be covered by a UF_{HK} of 4.2-7.1 and 0.1 percent would not be covered by a UF_{HK} of 7.3-14.5. While this study focuses on adults the results may apply even more strongly to infants and young children where inhalation may result in greater exposures per unit body weight, and metabolic systems, particularly MFO enzymes, are still under development.

Ginsberg et al. (2004) used PBPK modeling to evaluate the difference between neonates and adults in the metabolism of theophylline and caffeine. Both chemicals are metabolized by CYP1A2: caffeine to theophylline, theobromine, and paraxanthine; and theophylline to 3-methylxanthine, 1-methyluric acid, and 1,3-dimenthyluric acid. In neonates theophylline is "back" methylated to caffeine. Caffeine is cleared much more slowly in neonates than in adults (0.15 vs. 1.57 mL/kg-min, respectively) whereas theophylline is similarly cleared (0.35 vs. 0.86 mL/kg-min, respectively). The authors concluded that the extra back methylation path in neonates could largely account for the differences seen between neonates and adults. The results emphasize the importance of different metabolic pathways operating in neonates and infants during development.

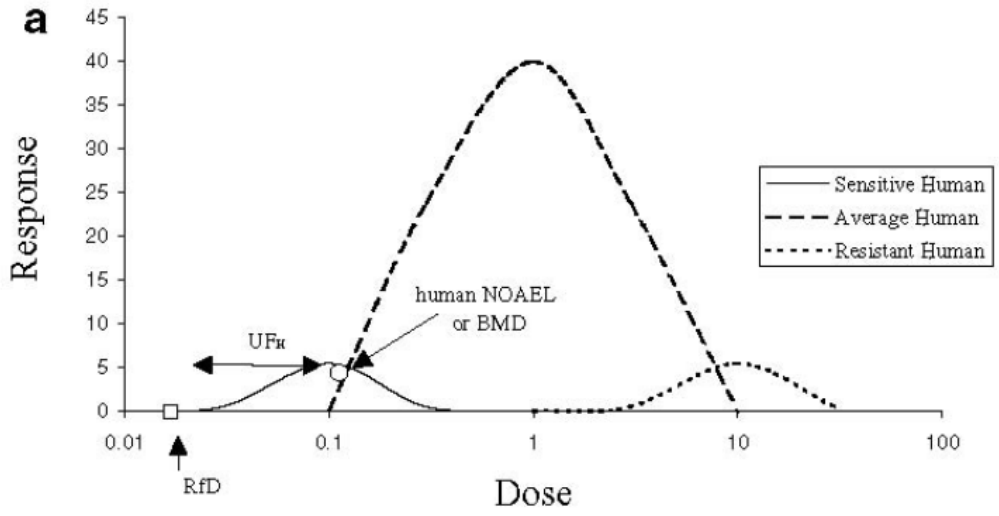
Gentry et al. (2003) evaluated the impact of pharmacokinetic differences on tissue dosimetry during pregnancy and lactation with PBPK modeling. Six chemicals were investigated: isopropanol, vinyl chloride, DCM, perchloroethylene, nicotine, and TCDD. Model predicted differences in dosimetry during pregnancy were largely the result of the development of metabolic pathways in the fetus or changes in tissue composition in mother and fetus. Generally, predicted blood concentrations were lower in the neonate during lactation than in the fetus during gestation. Predicted fetal/neonatal exposures vs. maternal exposures ranged from 2-fold greater (TCDD) to several orders of magnitude lower (isopropanol). The results of this study are in general agreement with earlier studies namely that the "age range of greatest concern is clearly the perinatal period. The most important factor appears to be the potential for decreased clearance of toxic chemicals … due to immature metabolic enzyme systems,".

Several aspects of the analysis by Dourson et al. *are questionable. Problems with their interpretation include the following*:

The paper confuses variability (i.e. measurable differences between individuals in a group or population), which <u>may</u> be represented by the log-normal distributions shown in their figures, and uncertainty (the range of plausible values for a parameter which has not been, or cannot be directly measured), which almost certainly is not distributed in this way.

OEHHA disagrees with the assumption that the "human equivalent response" distribution from which they identify a NOAEL has any relationship to the distribution of responses in an actual human population. If the study on which the derivation is based is in fact a human study (clinical or epidemiological), then this distribution may be reflective of a human population, although not necessarily the one of interest to the risk assessor. However, in the majority of cases the basis study is in animals. These data by definition contain no information about human variability, especially since the test animals are age-selected, and laboratory rodents in particular are genetically homogeneous and therefore much less variable than a human population.

Dourson et al.*'s Figure 6a (below) shows three distributions of response vs. dose for sensitive, normal and insensitive populations.*



The claim is that the normal UF_H based on a criterion (BMD or NOAEL) determined in the ***normal*** *population covers perhaps a 1000 fold dose range of the total human population including those of abnormal sensitivity. This example does not directly address the adequacy of the UF_H for determining a health protective exposure criterion for infants and children based on a toxicity observed in a normal human or animal study. In this figure, it is implied that at least half of the sensitive human subgroup (which could be young children) would respond at a dose ten times lower than the "average human".*

Even if the shapes of the actual dose/ response distributions shown in their Figure 6a resemble the assumed log-normal shape in the vicinity of the ED50, there are unlikely to be any data to support the conclusion that this shape is followed out to doses several decades above or below the ED50 as assumed by Dourson et al. (2002). Indeed, such very limited data as have a bearing on this question, such as distributions of common physiological or structural characters, imply the opposite: that the assumed distribution shape breaks down at extreme values.

In considering the interindividual differences between humans of different ages, the analysis by Dourson et al. is inapplicable because it assumes that the variability (and uncertainty) within the human population is represented by a single log-normal distribution. It has been emphasized so

often that it has become a cliché to point out that "children are not just small adults". A necessary corollary to this is that their susceptibility is not represented by merely a percentile within the overall adult distribution, but rather by an entirely separate (probably also log-normal) distribution with its own geometric mean and standard deviation or, rather, several such distributions reflecting the properties of different age groups having distinctly different susceptibility and variability. Especially for sub-groups such as infants, who have markedly different anatomical, physiological and biochemical characteristics from adults, this separate distribution may be widely separated from the log-normal distribution representing adults. This is in essence what we observed with our investigation of PBPK models with infant- or child-specific parameters.

The attempt to equate a reference exposure level with some specific frequency point on a distribution is intrinsically unsound. Not only are the actual distributions of variability and uncertainty generally unknown, and their additivity (or otherwise) not established, but the general objective in defining a reference exposure level is to select a level at which no effects are expected in the general population, not a level at which a specified low level of response such as 1% or 5% is expected. As noted in the document, a NOAEL is not a threshold, but rather an exposure level without observable response. Since these are usually based on animal studies, the response rate at the NOAEL can in fact range from 1% in a large study to 20% in a small one (Gaylor, 1992; Leisenring and Ryan, 1992). The assumption for non-cancer risk assessments is that there is a true threshold below which no responses are expected, and the objective in setting the reference exposure level is to choose a level below that threshold.

Comments of Kenneth Kloc Ph.D. on behalf of the West Berkeley Alliance, CBE and GCM

I am writing you today on behalf of the West Berkeley Alliance for Clean Air and Safe Jobs ("West Berkeley Alliance"), Communities for a Better Environment ("CBE"), and Global Community Monitor ("GCM"), in order to support OEHHA's proposal to:

- Update the Reference Exposure Levels ("RELs") for manganese, mercury, and arsenic/arsine, making these criteria generally more health protective

- Define 8-hour RELs for the above noted metals, as well as, formaldehyde, acetaldehyde, and acrolein (We also support the policy of setting 8-hour RELs for Toxic Air Contaminants in general, to insure that workers and school children are adequately protected)

- Lower the Acute REL for formaldehyde and to define an Acute REL for acetaldehyde

The above named organizations represent California residents who live in close proximity to stationary and mobile pollution sources that emit heavy metals and toxic organic chemicals into the air, thus increasing the chance for toxic exposures and subsequent health impacts.

Comment 1:

The West Berkeley Alliance, CBE, and GCM are particularly concerned that, under the current Chronic REL for manganese of 0.2 micrograms per cubic meter ($\mu g/m^3$), Californians are allowed to be exposed to manganese air concentrations four to five times higher than the levels that the U.S. Environmental Protection Agency ("EPA") and the Agency for Toxic Substances and Disease Registry ("ATSDR") have determined to be safe. (EPA's Reference Concentration for long-term exposure to manganese via inhalation is 0.05 $\mu g/m^3$, and ATSDR's Minimal Risk Level for manganese is 0.04 $\mu g/m^3$)

We are relieved that OEHHA now proposes to address this problem. Utilizing its new non-cancer risk assessment methodology, the agency has developed a more health-protective Chronic REL for manganese of 0.03 $\mu g/m^3$ and an 8-hour REL of 0.05 $\mu g/m^3$. The proposed RELs have the virtue of greater harmony with the federally developed health-based criteria noted above. They are also consistent with current scientific and regulatory opinion on the need for additional measures of safety in order to protect the young and other sensitive subpopulations. For example, the federal Food Quality Protection Act requires that the EPA use an additional safety factor of 10 to protect children in setting pesticide standards. California's SB 25 also recognizes that infants and children may be more sensitive than adults to toxic exposures and thus mandates that RELs be reviewed and revised as appropriate, to ensure that they are protective of this subpopulation.

The proposed RELs for manganese are based upon the same occupational epidemiology study used by the federal agencies to derive their manganese criteria. Similarly, the OEHHA RELs contain a cumulative uncertainty factor ("UF") of approximately three orders of magnitude, providing a large but reasonable margin of safety. Specifically, OEHHA applies a cumulative UF

of 2000, which is composed of specific UFs that extrapolate: (i) from a LOAEL to a NOAEL ($UF_L = 6$), (ii) from a subchronic to a chronic exposure ($UF_S = 3.16$), and (iii) from a healthy adult population to a potentially sensitive subpopulation of infants, children, and other groups ($UF_H = 100$).

Response:

This comment accurately describes OEHHA's current approach to the manganese RELs. It should be noted that, in response to other comments and to the availability of more detailed data than those in the published report by Roels et al. (1992), OEHHA has now revised the proposed manganese REL using benchmark concentration methodology. This avoids the necessity of extrapolating from a LOAEL to a NOAEL. It thus provides a REL value with improved confidence, although it is not in fact greatly different from that determined by the original method from the published summary data.

Comment 2:

Some commentators have criticized the simple multiplication of UFs in deriving health-protective exposure criteria as being overly conservative. They have reasoned that as more UFs are multiplied together, the probability that a person would fall simultaneously within the high end of the statistical distributions represented by these UFs becomes unreasonably low. However, several studies have looked at the issue of compounded conservatism in non-cancer toxicity criteria, and have shown that when the various uncertainties are treated in a more statistically sophisticated way, safety factors in the range of three orders of magnitude are reasonable. For example, Kodell and Gaylor utilized available toxicity databases to define probability functions for typical combinations of UFs, assuming that each UF is adequately represented by a log-normal distribution. They found that protecting the 99th percentile of a population for the case, $UF_L \times UF_S \times UF_H$, would require a cumulative UF greater than 1000.

The TSD (pg. 12) states that, "It is OEHHA's intent that the levels [i.e., RELs] will protect nearly all individuals, including those who are identifiable at the high end of susceptibility." Therefore, protecting people above the 99^{th} percentile of sensitivity, and preferably even higher percentiles, would be appropriate.

Response:

OEHHA staff agrees that multiplying the uncertainty factors together is not inherently over-conservative. This is particularly important when considering UFs that are intended to represent ranges of uncertainty, rather than variability. Although it is reasonable, and conventional, to represent the variability of parameters within a population by log-normal distributions, no such assumption can be made for the presumed likelihood distributions of parameter values based on uncertainty. As Kodell and Gaylor show, even in the case of variability-based distributions a multiplicative approach is needed to protect susceptible sub-populations with systematically different parameter values (such as infants or children), as opposed to some defined percentage of a single overall distribution.

Comment 3:

The largest part of the cumulative UF of the new manganese RELs is due to the UF_H. Its value is obtained by applying two UFs of 10 to occupational toxicity data in order to ensure that the most sensitive members of the population, including infants and children, are adequately protected against central nervous system damage. One of these factors of 10, the UF_{H-K}, is applied in order to capture the toxicokinetic variability of manganese in humans. This safety factor is reasonable given, as noted in the Technical Support Document, that: (i) newborns absorb more manganese from the gastrointestinal tract than do adults, (ii) neither the blood-brain barrier nor manganese homeostasis is fully developed in newborns, and (iii) infants and young children experience higher deposition of particles in the lung than do adults. Differences in manganese metabolism in the elderly and people with pre-existing health conditions are also likely to increase the range of toxicokinetic variability.

Response:

Comment noted.

Comment 4:

The other factor of 10, the UF_{H-D}, is applied to ensure that individuals having unusual biological sensitivity to manganese intoxication will also be protected. Again in this case, OEHHA's proposed UF_{H-D} is reasonable, given that the study upon which the REL is determined is of young men (average age of 30), who could represent a toxicologically resistant group having less variation in sensitivity than the population in general. In extrapolating this data to protect susceptible subpopulations, one should consider the "healthy worker effect," as well as, that the study sample did not include infants, children, women, the elderly population, and people with pre-existing disease conditions. Regarding the young, the developing brain of infants and children may be much more sensitive to manganese intoxication than the fully developed adult brain, as noted in the Technical Support Document. In addition, people with, or predisposed to contract Parkinson's Disease could be particularly vulnerable to manganese exposure (Health Canada, 2002). Given that the prevalence of Parkinson's in the U.S. is on the order one percent or more in people over age 65, this potentially sensitive subpopulation is relatively large.

Response:

The commentator independently summarizes considerations why a UF_{H-D} of 10 is reasonable given the current database on manganese toxicity.

Comment 5:

Dourson and Drinan have recently described a way of looking at human toxicological variability wherein the distribution of susceptibility in the general population is considered to be trimodal, having a resistant mode corresponding to the high end of exposure and a sensitive mode at the low end. In order to extrapolate a toxicological endpoint from a resistant subpopulation to a sensitive one, the authors note that a UF_H, "much greater than 10-fold, perhaps between 100- and 1000-fold or more," may be appropriate. Finally, as noted in the Executive Summary of the

Technical Support Document, the range of human sensitivity to non-carcinogenic toxicants has been modeled between 1 and 720, with the traditional UF_H of 10 representing only the 85th percentile of the range of sensitivity in the general population.

Response:

The commentator has interpreted the observations of Dourson and co-workers quite differently from some other commentators. Dourson and Drinan (2007) recapitulate observations from Dourson et al. (2002). According to comment 4 from Dr. Richard Becker (writing on behalf of the American Chemistry Council), "In Dourson et al., 2002, the authors explain how the 10X intraspecies UFH accounts for overall variability in the human population of 100- to 1000-fold." Thus it seems Dourson's conclusion is not obvious to all readers. OEHHA's specific concern is that in the case of neonatal and young infants, the UF_{H-k} of √10 is probably inadequate for inhalation exposure. A number of published analyses of human data and predictions from modeling indicate that an increase of the UF_{H-k} to 10 would be prudent in those cases where insufficient data are available. For example, the following studies support OEHHA's proposal. A limitation of the available data is that relatively few studies have focused on inhalation exposure and predictive PBPK analyses have limitations as well.

Renwick (1998) and Renwick et al. (2000) compared age-related differences in the pharmacokinetics of 36 drugs which are eliminated by different processes. Renwick et al. (2000) concluded that the main factor affected by age was the overall difference in clearance and the resulting elevated internal dose in neonates and children compared to adults. While these authors concluded that a UF_H value of 100 was not justified, they noted that an additional factor (>10) might be necessary in the case of a lack of developmental and reproductive toxicity data, inadequate data, or an irreversible toxic effect in neonates/young animals.

Dorne et al. (2001) evaluated the validity of the √10 UF_{HK} in relation to CYP1A2 metabolism using published data for clearance (CL), AUC and peak plasma concentration (Cmax) for caffeine, theophylline, theobromine, paraxanthine, and R-warfarin in human volunteers. The authors identified subgroups for which the √10 would be inadequately protective including about half of pregnant women, nearly all neonates, and 13% of infants. These drugs were administered orally or parenterally.

Ginsberg et al. (2002) also evaluated child/adult pharmacokinetic differences in the drug literature. These authors identified about 100 chemicals with some pharmacokinetic data and analyzed a subset of 45. Multiple regression analysis was used to evaluate relationships between age groups and mean pharmacokinetic parameter (Cmax, half-life, AUC, volume of distribution, clearance). In general, for many chemicals, early life stages appeared different in terms of clearance, half-life, and volume of distribution. The overall study results indicate that premature and full-term neonates tended to have 3 to 9 times longer half-life than adults for the drugs studied. Like the earlier work of Renwick et al. (2000) and Dorne et al. (2001) the drugs studied were administered orally or parenterally, not by inhalation.

Pelekis et al. (2001) used a PBPK model to derive adult and child pharmacokinetic UFs for a group of volatile organic compounds (VOCs). Adult models (50 and 90 kg) were compared with a 10 kg child model. Simulations involved continuous exposure to 1 ppm VOC for 30 days.

Arterial, venous and tissue concentrations of the parent VOCs were used to calculate Adult/Child values. For the Liver concentration metric the Adult/Child values were: styrene (0.033); xylene (0.037); trichloroethylene (0.061); dichloromethane (0.092); and chloroform (0.11). The model predictions indicate up to a 30-fold higher concentration of VOCs in child liver than adult liver. Unlike the drug studies above, this modeling study involves inhalation exposure of relevant environmental toxicants.

Jonsson and Johanson (2001) used a PBPK model of dichloromethane (DCM) to study the influence of metabolic polymorphism on cancer risk estimates. Exposure was by inhalation, and metabolism by glutathione transferase theta (GSTT1) and mixed function oxidases (MFO) occurred in lung and liver. The model was fitted to published toxicokinetic data on 27 male volunteers exposed to 250-1000 ppm DCM. Excess cancer risk resulting from lifetime exposures to 1-1000 ppm DCM was estimated using Bayesian and Monte Carlo methods. The relevant dose metric was DNA-protein cross links (DPX) in liver derived from DCM metabolized via the GSTT1 pathway. Data on the frequencies of the three GSTT1 genotypes (0/0, +/0, +/+) in the Swedish population were used in the analysis. The results indicated a large interindividual variability in estimated risk, even within the two metabolizing groups (+/0, +/+). The results indicate that the UF_{HK} of √10 for human PK variability may not be adequately protective for non-cancer endpoints. One percent of the population would not be covered by a UF_{HK} of 4.2-7.1 and 0.1 percent would not be covered by a UF_{HK} of 7.3-14.5. While this study focuses on adults the results may apply even more strongly to infants and young children where inhalation may result in greater exposures per unit body weight, and metabolic systems, particularly MFO enzymes, are still under development.

Ginsberg et al. (2004) used PBPK modeling to evaluate the difference between neonates and adults in the metabolism of theophylline and caffeine. Both chemicals are metabolized by CYP1A2: caffeine to theophylline, theobromine, and paraxanthine; and theophylline to 3-methylxanthine, 1-methyluric acid, and 1,3-dimenthyluric acid. In neonates theophylline is "back" methylated to caffeine. Caffeine is cleared much more slowly in neonates than in adults (0.15 vs. 1.57 mL/kg-min, respectively) whereas theophylline is similarly cleared (0.35 vs. 0.86 mL/kg-min, respectively). The authors concluded that the extra back methylation path in neonates could largely account for the differences seen between neonates and adults. The results emphasize the importance of different metabolic pathways operating in neonates and infants during development.

Gentry et al. (2003) evaluated the impact of pharmacokinetic differences on tissue dosimetry during pregnancy and lactation with PBPK modeling. Six chemicals were investigated: isopropanol, vinyl chloride, DCM, perchloroethylene, nicotine, and TCDD. Model predicted differences in dosimetry during pregnancy were largely the result of the development of metabolic pathways in the fetus or changes in tissue composition in mother and fetus. Generally, predicted blood concentrations were lower in the neonate during lactation than in the fetus during gestation. Predicted fetal/neonatal exposures vs. maternal exposures ranged from 2-fold greater (TCDD) to several orders of magnitude lower (isopropanol). The results of this study are in general agreement with earlier studies, namely that the "age range of greatest concern is clearly the perinatal period. The most important factor appears to be the potential for decreased clearance of toxic chemicals … due to immature metabolic enzyme systems".

As shown in Appendix E of the draft technical support document, OEHHA has also undertaken extensive work using PBPK modeling to support the conclusion that an appropriate default value for the $UF_{H\text{-}k}$ is 10, rather than √10 as implied by earlier practice.

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